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1 ✓ endocrine disorders

2 ✓ " glands (FW)

3 ✓ pituitary disorders

4 ✓ hypopituitarism (13) hyperpituitarism

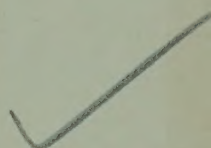
5 ✓ hyperpituitarism (14) childhood pituitary obesity

6 ✓ pubertas praecox

7 ✓ adrenal endocrine disorders

8 ✓ hypogonadism (9) progeria

10 ✓ thyroid gland (11) thymus



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ENDOCRINE DISORDERS IN CHILDHOOD
AND ADOLESCENCE



ENDOCRINE DISORDERS IN CHILDHOOD AND ADOLESCENCE

BY

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PREFACE

THE work represented by this book has been done in a busy general medical out-patient department, and this has put an additional strain on the staff. Therefore we are specially indebted to Dr. Jennings, Assistant Physician, Royal Berkshire Hospital, and to Dr. Tindall, Medical Registrar, and Dr. Kempton, Clinical Assistant, without whom nothing could have been accomplished. We are also indebted to Dr. Cave for radiographic reports and to Mr. Forder for photography under difficult circumstances. Kindly criticism and help has been given by Dr. Mills, Dr. Tindall, and Dr. Mawson, and very special thanks are due to Mrs. M. E. Mawson, Ph.D., for much help with the physiology. Professor Hugh Cairns, F.R.C.S., read a large part of the manuscript and his valuable suggestions were much appreciated. Mr. Wolters, M.A., Lecturer in Psychology, University of Reading, has given advice and help on all mental problems.

We have been handicapped by expense, which has prevented the full use of endocrine preparations, and the provision of a proper follow-up service. The nursing staff deserve our thanks for checking the attendance of patients as far as they could.

We acknowledge with many thanks permission from Dr. R. D. Lawrence, F.R.C.P., to publish the Line Ration Scheme and the two tables on pp. 88 and 90 from his book *The Diabetic Life*, 9th edition. From Engelbach's *Endocrine Medicine*, Vol. I, by courtesy of Charles C. Thomas, Publisher, Springfield, Illinois, we have been able to reproduce the measurement table. The table of commercial sex hormone preparations is reprinted by permission of the *Pharmaceutical Journal* (London), from their issue of January 4, 1941. Mrs. L. Read deserves many thanks for arduous secretarial work.

READING, December 1942

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CHAPTER 1

INTRODUCTION

THE rapid advance in knowledge of the function of the endocrine glands has given little time to arrange the essential facts to form a coherent whole. The terms endocrine and pituitary do not appear in the index of the 1924 edition of a well-known textbook of children's diseases, but we now realise the fundamental importance of endocrine balance in the growth, mentality, and reaction to disease of the individual and in the characteristics which are handed on to the next generation. Formerly the thyroid gland was given first place in the description of endocrine function, but the far-reaching researches of the last fifteen years have shown that the pituitary gland has even wider functions in regulating growth and development and in exerting an influence on every other ductless gland. This was one reason which, ten years ago, led us to search for endocrine disorder in every child who was sent to us for whatever cause. Two other events occurred at that time which focussed our attention on this branch of medicine: one was the observation of an unusual case of *pubertas praecox* (see p. 126); the other was the publication of Engelbach's *Endocrine Medicine*, a stimulating work to which we are greatly indebted. Two main theses run through this book: to show the value of repeated routine measurement, and to trace the subtle connection from one endocrine syndrome to another.

Since 1932 we have examined several thousand children and young adults, and the result of looking for endocrine disorder has far surpassed our expectations. A complete physical examination has been undertaken before resorting to the special technique used to estimate endocrine

disorder, for it would be useless to use hormones in such cases as renal dwarfism or coeliac infantilism without treating the underlying cause. Our experience has been gained in a general medical out-patient department, an advantage because the history and the established condition of the adult often indicate the significance of the earlier signs to be found in the child. We have therefore added examples from adult life where this was helpful and have not kept strictly to the confines of childhood. We have found that pituitary disorders in particular are relatively common and unrecognised, and the knowledge gained has thrown light on many clinical problems otherwise obscure. The progress of this study has revealed an ever-widening field, and opened up vistas of great interest.

The history of the individual as well as the history of the family merits careful consideration; for example, one patient who showed a growth defect due to anterior hypopituitarism had had a transient attack of diabetes insipidus at an early age. Another patient who was seen at the age of sixteen with signs of hypogonadism, such as irregular menstruation, undeveloped secondary sexual characteristics, and a typical tall thin build, gave a history that at the age of four years she was so fat that she was taken to see a children's specialist. The obesity gave place to extreme thinness at puberty. Observations such as these stress the importance of the routine system of measurements advocated in this book, and the close connection running through all endocrine disorders.

Endocrine disorder in the parents plays a large part in the endocrine make-up of the child; if the parents do not show evidence of dysfunction, it should be sought in the near relatives, for it may appear in only a few members of the family, possibly lying dormant in the others, to be awakened by some trauma, such as infection or pregnancy. In one family the mother and one daughter show pituitarism of the Fröhlich type and an aunt shows growth deficiency. The recognition of the pituitary dyscrasia that runs through a family such as this is of real value to the doctor and widens the conception of constitution or diathesis. So close

is the relationship between the ductless glands that a lack of hormonal balance may produce diabetes mellitus, pituitary disease, or thyroid disease in various members of the same family. In this respect recent research has shown the supreme importance of the anterior lobe of the pituitary gland, particularly in regulating growth and sexual function. Growth is stimulated throughout childhood by a powerful pituitary growth hormone, and the production of gonadal hormone at puberty depends on the action of the pituitary as also does the proper functioning of the sex organs, the thyroid, and the adrenals throughout life. Disorder in one gland will cause secondary changes in others, hypopituitarism, for example, leading to secondary hypogonadism at puberty, so that the picture is always complicated.

Infections are often the starting point of endocrine abnormality by causing depression of glandular function in those having a hereditary susceptibility; for example, a girl had a septic throat after tonsillectomy and shortly afterwards developed a typical Fröhlich's syndrome.

The endocrine balance of the individual has a close connection with mental stability. Mental shock may herald the onset of exophthalmic goitre, possibly by stimulating the production of the thyrotropic hormone of the pituitary. Some children tend to develop mentally and physically before their years and may have adult sexual feelings before the normal social inhibitions have developed, but in quiet surroundings these children tend to lose their excessive libido and thus avoid the problems of behaviour which might otherwise cause their appearance in a juvenile court.

The hormonal requirements of the foetus impose a strain on the maternal glands which these may be unable to meet successfully. It is not uncommon for multiparae to put on a considerable excess of weight during successive pregnancies owing to a defective thyroid stimulus to metabolism. Various degrees of hypothyroidism may be evident in the children, shown by overweight at birth and by delay in the appearance of the centres of ossification.

The effects of minor degrees of endocrine imbalance are so widespread that no doctor can afford to neglect them.

Convergent strabismus in infants should lead one to look for other evidence of hypothyroidism. Early or late appearance of the teeth and faults in their size, shape, arrangement, and calcification may be due to faulty internal secretions. The delayed dentition of hypothyroidism allows the central incisors to become large and widely spaced, so that the teeth arriving later become crowded out of place. In hypopituitarism the teeth are small and infantile in shape, and in hypogonadism the lateral incisors may be small or absent.

The detection of endocrine imbalance is more difficult in infancy and childhood than in adult life, because gross alterations from the normal have not taken place, but the earlier the diagnosis, the greater is the possibility of correcting the dysfunction and preventing the more serious conditions which arise in later life. With our present knowledge treatment is often empirical or experimental, but such great advances are taking place in the isolation and chemical analysis of hormones that therapy is becoming rational and scientific. We have had considerable experience in treating glandular disorders, and in general the results are better than one would expect. The family doctor is in an ideal position to detect the early abnormal traits in the individual and in the family and to carry out treatment. If he looks for the signs and symptoms described in the following pages, he will discover (as we did) a new subject of surpassing interest and practical value in dealing with his patients.

CHAPTER 2

PHYSIOLOGY OF THE ENDOCRINE GLANDS

AN adequate knowledge of the physiology of the ductless glands is absolutely essential for the diagnosis and treatment of endocrine disorder. Advances in this subject have been exceedingly rapid during the past few years and textbooks on the subject are out of date soon after publication. For this reason we have included a summary of the current ideas in endocrine physiology on which our outlook on the origin and treatment of endocrine disease is based. It is certain that in the future modifications will be made in these hypotheses affecting clinical as well as theoretical interpretations of the subject.

Physiology of the Pituitary Gland

The pituitary gland has so many functions and is so richly endowed with hormones affecting every phase of bodily activity that it must be regarded as the governor of the whole endocrine system.

The hormones of the anterior lobe are derived from its secretory cells, of which three types are recognised, differentiated according to their staining reactions into acidophil ($37\frac{1}{2}$ per cent), basophil (11 per cent), and chromophobe (52 per cent). Of these, the chromophobe cell is regarded as the mother cell from which the other types are developed by the formation of secretory granules having an affinity for either acid or basic stains ; it seems probable, too, that a diminution in the ability to take up the stains is reflected in an alteration of physiological cell activity, and that the chromophobe cell may represent a resting stage.

Clinical observations and experimental evidence both

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point to the acidophilic cells as the source of the growth hormone. They are present in greatest number and size during the period of life when growth is at its maximum and they diminish in number after middle age. In acromegaly, the general overgrowth of body tissue is associated with adenomata of these cells. Furthermore, Smith and McDowell (1), using a strain of dwarf mice which have no acidophil cells in the pituitary, were able to produce mice of the usual size by the implantation of normal glands. The basophil cells secrete hormones which stimulate the gonads. Cushing's syndrome, in which the development of virilism is a marked feature, is stated to be accompanied by a hyaline change in the basophil cells "which does not appear to be an expression of cell degeneration in the ordinary sense but is probably an expression of altered physiological activity" (2). This suggests that the masculinisation is due to a secretion from the basophil cells. During pregnancy, the pituitary gains 18 per cent in weight owing to enlargement of the anterior lobe, and special "pregnancy cells" appear which are apparently transitional mother (chromophobe) cells developing granules for a phase of secretory activity. There is also an increase in the number of the acidophil cells. After the termination of pregnancy, the pituitary reverts almost to normal, but at each succeeding gravidity this hyperplasia occurs again in order to cope with the enormous hormonal requirements of the foetus. After castration, hypertrophy of the anterior lobe takes place, this being due to increase in the acidophil cells and the formation of "castration" cells which are vacuolated basophil cells with the nucleus pushed to one side. The chromophobe cells do not show any evidence of the production of a physiological secretion. The effects produced by tumours of these cells can be accounted for by the pressure which they exert upon the surrounding structures (9).

The cells of the pars intermedia are faintly basophil and are believed by some to form the posterior lobe hormones "pitocin" and "pitressin" which influence the kidney and uterus.

The pars tuberalis, which is very small in adult man, constituting less than 2·6 per cent of the weight of the whole gland (3), is mainly composed of chromophobe cells (4) and its function is at present undetermined.

The pars nervosa or posterior lobe, which is derived from brain tissue, is composed of cells resembling neuroglial tissue but which have relatively more protoplasm than neuroglia. It also contains basophil granular cells which have probably infiltrated in from the pars intermedia and are thought to be the source of "pitocin" and "pitressin". In the whale, the posterior lobe develops without a pars intermedia and yet possesses these hormones (5): however, the argument by analogy that the human posterior lobe should also be the only source of these hormones is not conclusive.

The secretions of the anterior lobe pass into the general circulation by way of the vascular sinusoids and the arachnoidal sheaths of the blood-vessels. It is still a matter of dispute whether the posterior lobe secretions pass into the general circulation (6) or are discharged into the cerebrospinal fluid, as is believed by Cushing (7), who points out that the response to posterior lobe hormones injected into the ventricles is much more rapid than when it is injected into the blood-stream or given intramuscularly.

The supreme importance of the pituitary gland in regulating the other endocrine glands is fully recognised, but it is not yet known whether it produces a specific chemical substance for each of the glands which it stimulates or whether, as Collip (8) believes, the living pituitary forms no more than three hormones. Great difficulty is experienced in obtaining pure anterior lobe fractions and it is suggested (8) that the anterior lobe cells produce large parent protein molecules with prosthetic groups which have differing hormonal effects. It is not known how these prosthetic groups act upon the endocrine glands but the hypothesis is advanced that each organ is stimulated physiologically by the part of the protein molecule which it needs (10).

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Growth Hormone

One of the principal changes following hypophysectomy in animals is an immediate cessation of skeletal growth, although there may be an increase in weight in some cases due to deposition of fat. Cessation of growth, however, does not mean that no new cells are formed, for cell replacement is bound to proceed as long as the animal survives.

Evans and Long (11) first showed that the growth rate of normal animals was accelerated and giants were produced by giving alkaline extracts of the anterior pituitary. Later it was shown that similar extracts would cause resumption of growth in hypophysectomised animals (12). It should be emphasised that diet is an extremely important factor in determining growth (13) and that, despite the presence of sufficient amount of growth hormone, optimal growth cannot be obtained unless the diet is adequate.

A condition resembling acromegaly was produced in dogs by Benedict, Putnam, and Teel (14) by administering large amounts of pituitary extract over a long period of time. Enlarged pituitaries have been found in human acromegalics and, conversely, pituitary degeneration has been observed in Simmonds's disease in which there are splachnomieria and a gradual shrinkage of the whole body with a loss of up to 40 per cent of the body weight. In the consideration of clinical conditions and the earlier experiments with animals one should not attribute all the symptoms observed to the presence or absence of growth hormone. Crude extracts of the gland were used which almost certainly contained other factors. Clinical acromegaly may or may not involve an increase in the other functions of the pituitary, and Simmonds's disease seems to be caused by a general destruction of the pituitary which interferes with sexual function, for example, as well as growth.

In the earlier experiments, growth was judged merely by an increase in weight, and recently detailed studies of the effects of purified extracts on the skeleton have been made. Freud, Levie, and Kroon (15) found that extracts practically free from prolactin, corticotropic, and thyrotropic

activity, if given immediately after operation, prevented the epiphyseal closure which followed hypophysectomy and maintained normal growth. The site of action of growth hormone is considered to be the proliferating cartilage. These authors also point out that optimal body growth must require the synergism of all the hormones.

The growth hormone is greatly influenced by the sex hormones found in the gonads. The administration of oestrone has been found (19) (16) to inhibit the natural increase of body weight and length in immature rats and mice for as long as it is given, growth being resumed with cessation of treatment. The arrest of bone growth is thought to be due to an antagonistic action between oestrone and growth hormone occurring at the epiphyseal junction and not to direct interaction between the two hormones. A similar condition was produced by the synthetic oestrogenic compound diethylstilboestrol (19), but with this substance it was noted that the arrest of growth was permanent owing to the production of abnormalities in the cartilage cells. This latter observation is not without significance in the treatment of human beings by oestrogenic therapy. Clinically, the antagonistic effect of gonadal hormones upon growth is seen in cases of *pubertas praecox*, where the body is flooded with sex hormone, with resultant early fusion of the epiphyses and a check in the increase of bodily length, p. 127. In normal children the sex hormones are secreted in small amount until puberty, but thereafter they are increased and skeletal growth begins to slow up. Although skeletal growth is inhibited by the sex hormones, the full development of the muscles appears to be dependent upon the presence of male sex hormone, for it has been shown that generalised muscular hypertrophy is produced in both male and female guinea-pigs by the injection of a potent male hormone (18). This is also paralleled by the development in *pubertas praecox*, where the muscular strength may be out of all proportion to the age of the patient, p. 128 (17).

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Gonadotropic Hormones

The secretion of the anterior pituitary gland is necessary for the normal functioning of the gonads of both sexes. If the pituitary is removed there is a considerable decline in the weight of the ovary which is coincident with a decreased number of follicles and is accompanied by involutionary changes in the endometrium and vagina. The administration of pituitary extracts will prevent these changes, but only if given within a short period of hypophysectomy. Subsequently it has little or no effect. Similarly regression and atrophy of the testis and accessory organs occur in the male after hypophysectomy, and these changes may also be prevented by administration of pituitary extracts. Extracts from a female pituitary are just as effective as those from a male and it is therefore likely that gonadotropic hormone is not specific for either sex, but depends on the particular properties of the male or female gonad.

The presence of two gonadotropic hormones in the pituitary is fairly well established. One of these stimulates follicular growth and maturation and is known as the follicle-stimulating hormone (F.S.H.). The other stimulates the conversion of the cells of the membrana granulosa and thecae into lutein cells and is called the luteinising hormone (L.H.). Both of these hormones are believed to be essential for ovulation, corpus luteum formation, and pregnancy. If L.H. is injected with or before F.S.H. the effect of the latter is greatly augmented, although L.H. itself does not produce any increase in the weight of the ovary (1). L.H. given after F.S.H. causes luteinisation.

In males F.S.H. is believed to stimulate the germinal epithelium of the testis and has no effect on the secondary sex organs, while L.H. maintains the interstitial cells which elaborate the male hormone and in turn causes enlargement of the secondary sex organs and development of the secondary sex characteristics. Evans (2) has recently postulated an "interstitial cell stimulating" hormone (I.C.S.H.) which stimulates the interstitial tissue of ovary and testis and which he believes to be distinct from L.H. This view, however, has not yet gained general acceptance.

The injection of oestrogen has effects on the pituitary which depend on the size of the dose and the length of the period of treatment. Small doses are believed to increase the rate of secretion of L.H. but not of F.S.H. (3). Larger doses diminish the secretion of both hormones. Oestrogens seem to have no direct effect on the ovary, but when injected over a prolonged period result in ovarian atrophy due to inhibition of the production of gonadotropic hormones. Androgenic hormones (4) also exert a depressing effect on the pituitary but are far less potent in this respect than oestrogens (5).

Gonadotropic hormones injected into animals over a long period gradually cease to stimulate the gonads and eventually cause atrophy. This is said to be due to the production of "anti-hormones" which can be detected in the blood-serum and which neutralise the effect of the injected hormone (6). On the other hand there is evidence

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that the body does not produce anti-hormones to inhibit excessive secretion by its own pituitary gland. Until gonadotropic hormones are prepared in a pure state the mechanism of anti-hormone formation is likely to remain somewhat obscure. In any case no large amounts of anti-gonadotropic substance are found in humans following treatment with gonadotropic extracts and it is possible to continue the treatment for several months without causing a phase of insensitivity or damaging the gonads.

Substances resembling the pituitary gonadotropic hormones are excreted in the urine in pregnancy and certain other conditions. Formerly it was considered that two "pituitary-like" hormones, prolan A and prolan B, occurred in pregnancy urine, but it is now believed that there is only one prolan which originates in the chorionic epithelium (7). It resembles L.H. in that it stimulates the interstitial cells of the testis and causes hypertrophy of the accessory sex organs in males and causes luteinisation of the ovaries in females. A follicle-stimulating effect may be obtained with prolan in intact but not in hypophysectomised animals, and the result is therefore considered to be due to the action of the animal's own pituitary. It is on this effect that the Aschheim-Zondek and Friedmann tests for pregnancy are based. A positive test is obtained between two and ten days after the missed period depending on the individual variation in the length of time occurring before implantation of the ovum. The amount of prolan then rises and enormous amounts are observed between the fiftieth and sixtieth day (up to 300,000 rat units per litre). Subsequently the secretion declines.

A hormone similar to prolan is secreted in association with certain neoplasms, particularly hydatidiform mole, chorionepithelioma, and teratoma. In the first named, tremendous amounts may be excreted. A positive Aschheim-Zondek test is obtained in these conditions, and the persistence of a positive result after the removal of a chorionepithelioma indicates the presence of metastases before they can be diagnosed clinically (8).

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Thyrotropic Hormone

In addition to the failure of growth and sexual function which occurs in hypophysectomised animals there is a considerable fall in the basal metabolic rate due to inadequate functioning of the thyroid gland. The gland becomes atrophied and decreases in weight. The epithelium degenerates and the follicles are distended with densely staining non-vacuolated colloid. These changes are due to a lack of thyrotropic hormone, the function of which is to maintain the activity of the thyroid gland and to facilitate the discharge from it of the thyroid hormone. The symptoms of thyroid deficiency in hypophysectomised animals (lowered B.M.R. and hypoglycaemia) are similar to those which occur in clinical hypopituitarism.

If pituitary extracts are administered to hypophysectomised animals these changes are prevented, and if they are given to normal animals the results are the reverse of those following hypophysectomy. The epithelial cells of the thyroid gland are hypertrophied, the vesicles decrease in size and the colloid becomes vacuolated. The B.M.R. is increased and exophthalmos may occur (1). The latter, however, is not invariable and it is not certain that it can be attributed to the action of the thyrotropic hormone.

As in the case of gonadotropic hormones, prolonged treatment with extracts containing thyrotropic hormone leads to the production of "anti-hormones" in the blood (2). These anti-hormones will inhibit the action of thyrotropic

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hormone in guinea-pigs, but owing to species specificity the clinical application is limited. "Anti-hormones" to pure thyrotropic hormone have not, of course, been produced as the pure hormone has not yet been isolated. The purest extracts are at present contaminated with gonadotropic hormone. The action of thyrotropic extracts may also be inhibited by giving iodine (3), but this appears to be due to prevention of the liberation of thyroxine from the thyroid rather than to an effect on the thyrotropic hormone itself.

Partial removal of the thyroid gland is followed by a compensatory hypertrophy which is believed to be due to the thyrotropic hormone. Complete thyroidectomy causes hypertrophy of the anterior pituitary gland.

The injection of small amounts of oestrin for short periods appears to have variable effects on the thyroid, but large doses given over long periods cause degeneration which has been attributed to inhibition of secretion of thyrotropic hormone. With this in mind Kirklin and Wilder (4) have administered oestrin to human acromegals and obtained reduction in the severity of the symptoms.

Thyroid substance itself is also thought to inhibit secretion of thyrotropic hormone by the pituitary. As one of the results of rapid metabolism which occurs in infectious fevers, there is increased thyroid activity and it has been claimed that there is a raised amount of thyrotropic hormone in the blood (5).

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Adrenocorticotropic Hormone

The anterior pituitary gland is believed to secrete a hormone which is necessary for the maintenance and functioning of the adrenal cortex. In hypophysectom-

ised animals the adrenal medulla is not affected but the cortex becomes atrophied. Both the zona glomerulosa and the zona fasciculata are affected, and according to Moon (1) there is a rapid loss of lipoids from the outer layer of the zona fasciculata. The administration of pituitary extracts prevents these changes and may even cause cortical hypertrophy and deposition of lipoids in the outer part of the zona fasciculata. Administration of pituitary extracts to normal animals has similar effects.

Compensatory hypertrophy of one adrenal gland after removal of the other is ascribed to activity of the adrenocorticotrophic hormone (2). It does not occur in completely hypophysectomised animals. Thyroidectomy does not interfere with this hypertrophy (3). Selye and Collip (4) found that doses of oestrin cause hypertrophy of the adrenal cortex in the rat. According to Ingle and Kendall (5) administration of cortical extract causes adrenal cortical atrophy, but this may be prevented if adrenocorticotrophic hormone is given at the same time. Recently the presence of sex hormones in normal and pathological adrenals has been demonstrated and it has been found that extracts containing adrenocorticotrophic hormone not only enlarge the adrenals in infantile or hypophysectomised rats of both sexes but produce effects after castration of such animals which are ordinarily attributed to sex hormones, viz. oestrus and enlargement of the male organs (6). There is much yet to be learned concerning adrenal-pituitary relationships, especially that between pituitary and adrenal medulla which is at present very obscure.

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The Anterior Pituitary Gland and Carbohydrate Metabolism

The relationship between the anterior pituitary gland and carbohydrate metabolism is not very clear, but that such a relationship exists has been shown in many experiments. Animals from which the pituitary has been removed are remarkably sensitive to the action of insulin which may easily cause a fatal hypoglycaemia (1). Furthermore, the experimental diabetes caused by pancreatectomy is ameliorated by hypophysectomy (2). Administration of extracts of anterior pituitary relieves the sensitivity of the hypophysectomised animal and restores the diabetic condition in hypophysectomised depancreatectomised animals (3). Recently extracts of anterior lobe have been found to produce permanent diabetes with hydropic degeneration of the beta cells of the islet tissue and decreased insulin content of the pancreas. The active principle which acts immediately to prevent the fall in blood-sugar in hypophysectomised animals when insulin is given has been termed the "glycotropic" factor (4) as distinct from the truly "diabetogenic" factor, which after a latent period of several days produces the typical diabetic symptoms of glycosuria, ketonuria, and polyuria.

Anterior pituitary extracts have also been found to produce ketonuria in fat-fed rats and a rapid deposition of fat in the liver (5) (6). It is not certain whether or not this is part of the diabetogenic effect. Another principle known as the "glycostatic" substance is thought to act on the muscles to depress the rate of carbohydrate oxidation (7). Long (8) has recently conducted experiments which indicate that the presence of functional adrenal cortical tissue is essential for the diabetogenic action of the pituitary.

It has been suggested by Anselmino *et al.* (9) that the development and function of the islet tissue are governed by a "pancreatotropic" hormone of the pituitary, and although the matter is still controversial, Marks and Young (10) have recently demonstrated marked hypertrophy of islet tissue in rats treated with crude pituitary extracts.

If the experimental results can be applied to human diabetes it is possible that certain cases may be due to over-production of a pituitary hormone. "Insulin-resistance" exhibited by some patients may be due to an excess of the glycotropic factor. Other cases showing no signs of pituitary dysfunction may also be of pituitary origin, for only a short period of diabetogenic hyperactivity might be sufficient to cause a permanent change in the islet cells (11) (12).

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The Anterior Pituitary Gland and Lactation

In preparation for the eventual secretion of milk, the nipples, ducts, and glandular tissue of the breasts of female children undergo development at puberty as the result of stimulation by the ovarian hormones oestradiol and progesterone. From experiments with intact animals it has been concluded that this is a direct stimulation by these hormones of the mammary gland and that oestradiol affects the conducting, and progesterone the secreting mechanism. More recent evidence suggests that the development of the mammary gland cannot take place in the absence of the pituitary gland. Gomez and Turner (1) believe that the ovarian hormone may stimulate the production by the pituitary of a hormone which is responsible for mammary development and which they have called the mammogenic hormone. There is, too, the possibility that mammary

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growth may be promoted by stimulation of the adrenal cortex, for it has been shown that progesterone can be isolated from the adrenal cortex (2) and that desoxycorticosterone, a hormone present in the adrenal cortex, causes development of breast tissue (3).

In animals in which the breasts are fully developed the initiation and maintenance of lactation are controlled by a specific lactogenic hormone (prolactin) which is secreted by the anterior lobe of the pituitary gland. It seems possible that other anterior lobe factors also play a part in enhancing established milk secretion (4). Normally lactation does not begin until oestradiol and progesterone disappear from the circulation and the corpus luteum undergoes its post-parturient involution. The pituitary lactogenic hormone is then found in increasing amounts and stimulates the production of milk by the mammary tissue. Normal milk production can only be maintained if the adrenal cortex and the thyroid gland are intact, for deficiency in either factor will lessen or prevent lactation (4). Injection of oestradiol or testosterone inhibits the production of lactogenic hormone and may be used clinically where necessary to suppress the secretion of milk (5).

In the past the chief method of assay of the lactogenic hormone has been by determining its effect on the growth of the crop gland of the pigeon. All workers, however, do not agree that the factors which cause crop growth in pigeons and lactation in mammals are identical (6), and extracts assayed both on mammals and on pigeons do not always give the same results. The pigeon method has been preferred because it is comparatively easy to carry out, but it would seem to be more satisfactory if extracts for clinical use could be assayed on mammals. It has recently been reported that the lactogenic hormone of the pituitary has been prepared in a crystalline protein form (7) (8).

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The Posterior Pituitary Gland

There has been much controversy as to whether the posterior pituitary is a true secretory gland. It has been claimed that the active extracts obtained from it are of purely pharmacological interest. However, recent evidence confirms the secretion by the pituitary of a hormone inhibiting diuresis ("pitressin", "vasopressin"). This hormone is believed to control the reabsorption of water from the renal tubules after filtration through the glomeruli (1). In the case of dehydration or excessive salt intake the hormone is secreted at an increased rate which results in a greater absorption of water. Teel and Reid (2) claim that a similar anti-diuretic material can be obtained from the urine of eclamptic patients and that it is responsible for water retention in this condition. The secretion of this hormone is believed to be controlled by the supra-optic nuclei of the hypothalamus, and if the nervous connections of the posterior pituitary are severed, the kidneys are unable to concentrate the urine and a condition resembling diabetes insipidus results. Extracts containing the anti-diuretic principle are also believed to have certain cardiovascular effects such as constriction of the smaller arteries and arterioles and elevation of the blood-pressure. Intestinal peristalsis is also stimulated. The physiological significance of these effects is not, however, as well established as the anti-diuretic action.

Other extracts of the posterior pituitary cause contraction of the uterine muscles ("pitocin", "oxytocin"), the effect being maximal at parturition when the uterus is sensitised by oestradiol. Since oestradiol also increases uterine motility they may act synergistically. On the other hand, parturition has been found to occur normally in animals from which the posterior pituitary has been removed.

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The Gonads

The Testis

The testis produces an external secretion containing the spermatozoa, which are derived from the germinal cells lining the convoluted seminiferous tubules and an internal secretion containing the male sex hormone or hormones, derived from the interstitial cells of Leydig and possibly the cells of Sertoli.

Normally, the testes have descended into the scrotum at the eighth month of intrauterine life and at the age of puberty have reached a stage of development when normal spermatozoa are produced. If testicular descent is not accomplished at all, there is failure in development of the spermatozoa and the individual is nearly always sterile; this lack of fecundity, however, is not always accompanied by a eunuchoid appearance, for the cells responsible for the formation of male hormone may remain unaffected and the secondary sex characteristics appear.

The interstitial cells of Leydig, from which the male hormone is formed, are modified fibroblastic cells appearing in groups in the connective tissue supporting the seminiferous tubules. They form a large part of the testis during the middle period of intra-uterine life, decrease at birth and increase at puberty: they are present in greatest number from the age of 10 to 19 years and subsequently diminish. During intra-uterine life and up to 2 years of age, they contain a considerable amount of lipoid; at puberty they again increase in size and lipoid content is greater, a fact that is of interest when one remembers that the lipoid extracts of testicular substance contain male hormone. In adult life Leydig's cells contain crystalloids and some pigment.

The male hormone testosterone is a sterol and has been synthesised from cholesterol (1). Altogether, some fifty

allied compounds have been prepared having varying degrees of male hormone activity (2). Testosterone undergoes oxidation in the body and is excreted in the urine as dehydroandrosterone and androsterone, which are physiologically less active. Only a small amount of administered testosterone, however, is excreted in this way (3). Adrenal extracts have been found to possess androgenic potency (4) and androsterone has been isolated from the adrenal gland (5). Large amounts of androgenic material have been found in the urine of women suffering from virilism associated with an adrenal tumour but not in other types, and hence its appearance may be of diagnostic significance (3). An androgenic compound may also be derived from the female gonad, as was demonstrated by Hill (13), who, grafting ovaries into the ears of castrated male mice, showed that there was occurrence of masculinising hormones whose activity could be made to decrease or increase with the application or removal of heat.

The testicular hormone, which, as we have seen, is controlled by the anterior pituitary, brings about the development of the secondary sex characteristics at puberty. There is enlargement of the external genitals and of the seminal vesicles and prostate with ability to ejaculate the semen; libido and potency are stimulated; growth of hair occurs in the pubic and axillary regions, on the face, and to a lesser degree on the body; the muscles increase in size, the larynx develops, the epiphyses close, the bones become thicker, and the distribution of fat is altered. The testicular hormone maintains these characteristics throughout adult life. At puberty also, spermatozoa are formed for the first time under the influence of the follicle-stimulating hormone of the anterior pituitary.

Early castration in the male prevents the growth of the penis, prostate, and seminal vesicles and the enlarged larynx remains of an infantile type, the voice remaining high-pitched. The epiphyses may remain open and, as the growth hormone is not inhibited by gonadal secretions, long bone growth becomes excessive. Castration in adult life leads to a reversal of most of the pubertal changes. The skeleton, however, remains unaltered and the size of the penis is normal.

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Ligation of the vas deferens leads to degenerative changes in the germinal epithelium of the testis but the interstitial cells persist and continue to secrete the testicular hormone so that the secondary sex characteristics are maintained.

In animals, castration is followed by changes similar to those occurring in man. In addition, the appearance of "castration cells" and an increase in the chromophobes in the anterior pituitary have been observed. The adrenals and thymus are enlarged and excess of gonadotropic hormone appears in the urine. These changes may be reversed by administration of male hormone. In immature male animals the onset of puberty may be hastened by administration of testosterone.

The maturation of the skeleton and closure of the epiphyses are probably not functions of testosterone itself, for McCullagh (6) observed that the appearance of secondary sexual characteristics in a case of severe hypogonadism treated with testosterone propionate over a period of sixteen months did not coincide with any change in epiphyseal development, which remained ten years behind the chronologic age of the patient. It has been suggested recently that oestrogens may play an important part in epiphyseal closure in both sexes (7).

Enlargement of the scrotum with early testicular descent has been brought about in macaque monkeys by giving testosterone propionate (8). In human beings certain cases of cryptorchidism react favourably to this treatment, growth and descent of the testis being produced.

Spermatogenesis is influenced by the pituitary and is apparently not increased by the use of male hormone, and a prolonged series of injections into rats has been found to cause a decrease in the weight of the testis, probably due to depression of pituitary function and a consequent lack of gonadotropic hormones which are responsible for the growth and functions of the sex organs. It is interesting in this connection to note that in hypophysectomised animals testosterone will maintain spermatogenesis, but only if given immediately and not if any degeneration of the germinal epithelium has occurred (9).

The loss of potency and libido which sometimes occurs in men at about 50 years of age, possibly accompanied by failing mental and physical ability, has been greatly relieved by giving testosterone propionate to replace the natural hormone. If treatment is stopped, conditions soon revert to the previous state (10) (11). In younger patients, and particularly if there is any chance of recovery of pituitary function, it would seem wise to give prolonged and full dosage of gonadotropic hormones before supplying the missing hormone. This has, at any rate, the merit of being one step nearer the natural physiological method of producing gonadal hormones and their effects.

Esterification of male hormone greatly increases its potency, and the effects of administration are considerably prolonged and rendered more continuous by injection in oil or implantation under the skin. It may be absorbed percutaneously when it is made up in an alcoholic or oily base and rubbed into the skin. This method is particularly adapted to the giving of maintenance doses and is effective in producing the required physiological results (12).

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The Ovary

As a result of stimulus by pituitary gonadotropic hormone the ovary produces oestradiol, to which the female organism owes its feminine characteristics. Oestradiol and the other sex hormones progesterone and testosterone are

sterols and are closely related chemically. Two other oestrogenic substances, oestrone and oestriol, which are found in urine, are considerably less potent than oestradiol. Other very dissimilar substances have been found by Dodds (1) to be active, and one of them, diethylstilboestrol, which has activity equivalent to that of oestradiol, is being used clinically. The relationship between chemical constitution and physiological activity is at present obscure.

Oestradiol is frequently referred to as the follicular hormone since it is normally produced by the theca interna of the ovarian follicles regardless of size (2). In pregnancy, however, large amounts of oestrogenic substance are produced by the placenta. Oestrogenic material has also been found in the adrenal glands (3) and in the testes (4) (5).

Oestradiol is responsible for the development of the female accessory sex organs and secondary sex characteristics at puberty. Under its influence the female body is adapted for the bearing of children. The uterus, vagina, and Fallopian tubes are enlarged and the mammary glands undergo development. The menstrual cycle is initiated and maintained until the menopause. The curves of the body become rounded and hair appears in the axillae and on the pubes. If the ovaries are removed, menstruation ceases and the uterus becomes atrophied. At puberty, the ovarian hormone inhibits growth and promotes epiphyseal closure. That the effect of oestradiol on the secondary sex organs is a direct one is shown by the fact that it will produce mitoses in the cells of these organs (6). Certain other oestrogenic effects may be produced through the pituitary.

Oestradiol is believed to be converted in the body to oestrone and oestriol, which are excreted in the urine. The conversion of oestradiol to oestrone can only take place in animals with ovaries and the presence of a functional uterus is necessary for the further change from oestrone to oestriol. Progesterone facilitates the latter change and also increases the amount of oestrogen excretion, possibly by preventing the destruction of oestrogens in the body. When the corpus luteum is functional, as in the luteal phase of the menstrual

cycle or in pregnancy, more oestriol than oestrone is excreted (7) (8) (9).

Deprivation of the female hormone caused by ovariectomy results in atrophy of the uterus and vagina, deposition of fat around the shoulders and pelvic girdle, and cessation of menstruation. Both re-development of the genitals and menstruation have been produced in doubly ovariectomised women by administration of oestradiol and progesterone (10) (11) (12). At the time of the climacteric the ovaries become smaller, the Graafian follicles disappear and there is a great reduction in the amount of oestradiol produced. Menstruation then ceases, there is some degree of recession of the secondary sex characteristics, with occurrence of irregular vasomotor control and sometimes mental disturbances, pruritus, and kraurosis vulvae. Oestrin therapy is of great value at this time. Occasionally, possibly as the result of a disturbance of hormonal balance in favour of an androgenic hormone, the personality and physical appearance tend to become masculine.

It has been found that esterified oestradiol is physiologically more active than the free hormone and oestradiol benzoate is frequently employed. Subcutaneous implants of hormone tablets will give increased activity over a considerable period (13). Oestrogens applied to the skin as ointments or creams are effectively absorbed (14) and applications to the breasts have produced increased effects locally. MacBryde, by inunction of oestradiol benzoate into one breast, produced considerable unilateral growth in ten days, and the same treatment when applied to the other side caused a similar increase in size. Omission of the treatment was followed by "withdrawal bleeding" and rapid regression in the size of the breast (15). The oral effectiveness of oestrogens is well established and it has been found that oestriol glucuronide is ten times as effective orally as subcutaneously (16).

Prolonged administration of oestradiol to guinea-pigs leads to the formation of uterine fibromata which continue to grow as long as the hormone is acting but regress when it is withdrawn (17) (18). This tumorigenic activity of oestradiol is antagonised by progesterone and testosterone (20) (21).

Excessive doses of oestrogens produce in the uterine epithelium of rats metaplasia which can be prevented by simultaneous administration of progesterone (18). It has been suggested that treatment of uterine fibromata in human beings with progesterone, thyrotropic hormone, or testosterone might prove beneficial (19), and recently it has been found that considerable clinical benefit may be derived in cases of menorrhagia due to fibroids by the subcutaneous implantation of testosterone propionate, although there appears to be no effect produced in the fibroids themselves (22). It is believed that malignant epithelial growths cannot be induced in the uterus and vagina by excessive doses of oestrogens. The production of mammary tumours in mice is favoured by oestrogens only where there is a high hereditary incidence of spontaneous cancer.

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Menstruation.—At the commencement of each menstrual period, one of the Graafian follicles and the ovum within it begin to increase in size and the follicular fluid contains the hormone oestradiol. It is believed that this process is initi-

ated by the secretion of the follicle-stimulating hormone of the anterior pituitary. The amount of oestradiol secreted increases rapidly and produces a hyperplasia of the uterine glands and thickening of the mucosa. At about the sixteenth day, the follicle bursts and the extruded ovum, covered by a layer of nutritive cells, enters the Fallopian tube. After rupture, the walls of the follicle collapse and blood extrudes into the remaining cells which become covered with a yellow pigment called lutein and form the corpus luteum. This body grows in size and, under the influence of the luteinising hormone of the pituitary, produces progesterone, which prepares the uterine endometrium for reception of the ovum. At the same time, the secretion of oestradiol, which reached a peak at the time of ovulation and then fell off, increases again (1). Oestradiol is produced by the corpus luteum. If fertilisation of the ovum does not occur, the secretion of both hormones falls off abruptly, presumably because pituitary stimulation ceases, the superficial and middle layers of the uterine mucosa disintegrate, and bleeding occurs. The hormonal factor which induces bleeding is the sudden deprivation of oestradiol and progesterone but the intermediary mechanism between the two is not known. Sometimes the follicle fails to rupture and degenerates, no corpus luteum being formed. As the secretion of oestradiol falls off, bleeding will occur just as in normal menstruation, but as no ovum has been extruded the individual is sterile. Such anovulatory cycles occur frequently in monkeys and are also found in human beings. The method of Browne and Vening (2) for determining the amount of pregnanediol in the urine may be used to investigate causes of sterility. If no corpus luteum is formed, no progesterone is produced and no pregnanediol is excreted in the urine. It should be borne in mind, however, that in some cases progesterone may be secreted by the adrenal cortex (3). Recently, the difference in electrical potential between the vagina and abdominal wall has been followed both in animals and in women and a marked change in potential was found to coincide with ovulation as shown by laparotomy (4) (5).

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Pregnancy.—Following fertilisation, the ovum is embedded in the uterine endometrium which has been prepared and sensitised by the action of progesterone. The corpus luteum persists and continues to produce progesterone until the end of pregnancy. Both oestradiol and progesterone are necessary for the growth of the uterus, to accommodate the growing foetus, but other factors must be involved as well, for it is not possible to produce uteri of comparable size in non-pregnant animals by treatment with these hormones (1). In most animals, ovariectomy or the removal of the corpus luteum during pregnancy results in abortion but this is not necessarily the case in the human. This does not mean, however, that oestradiol and progesterone are not required for the maintenance of human pregnancy, for oestradiol is certainly produced by the placenta and progesterone may also come from a non-ovarian source. Clinically, corpus luteum extract administered in certain types of endocrine dysfunction will prevent recurring abortions and enable the foetus to be brought to term. Large amounts of oestradiol given during pregnancy result in abortion, probably by inhibiting production of luteinising hormone by the pituitary.

In all mammals the term of pregnancy is a multiple of the sexual cycle of the species. Parturition is believed to be influenced more by hormonal factors than by mechanical distension of the uterus, changes in the foetus, or senility of the placenta (2). Pregnancy may be prolonged by injection of progesterone or prolan but only for a short period, and then the foetus dies (3) (4) (5).

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Progesterone.—Progesterone is produced by the corpus luteum under the influence of the luteinising hormone of the anterior pituitary. It is a sterol, allied to testosterone, and this chemical relationship probably accounts for the fact that testosterone, when given to women, has an action somewhat similar to that of progesterone (1). Progesterone is formed whenever a functional corpus luteum is present, i.e. in the latter part of the menstrual cycle and in pregnancy. Its production is at a maximum in the eighth month of pregnancy and falls abruptly before parturition (2). As in the case of the other sex hormones, progesterone has been found in the adrenals. Callow and Parkes (3) showed that adrenal extracts of some animals produce progestational proliferation, and more recently crystalline progesterone has been isolated from the adrenal gland (4). Progesterone is also secreted by the placenta, as is shown by the presence of its excretory products in the urine after removal of both ovaries during pregnancy (8).

The chief functions of progesterone are the preparation of the uterus for reception of the ovum and its maintenance during pregnancy. It causes the development of the endometrium of the uterus, whereas the growth of the myometrium is produced through the action of oestradiol. Progesterone also depresses uterine motility, and oestradiol on the contrary causes rhythmic contractions of the uterus. Ovulation during pregnancy is inhibited by progesterone, probably by preventing the production of follicle-stimulating hormone by the pituitary.

Progesterone is eventually excreted in a modified form in the urine. Provided that a functional uterus is present, the progesterone is converted to pregnanediol which is then conjugated with glycuronic acid by the liver and excreted by

the kidneys as the water-soluble glycuronide. The latter can be isolated and determined gravimetrically as the sodium salt (6) (7). The appearance of pregnanediol coincides with the luteal phase of the menstrual cycle and it is also produced in large amounts in pregnancy. Abnormally large amounts of pregnanediol have been found in women with adrenal virilism (5).

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The Adrenal Glands

Since the experiments of Brown-Séquard in 1856, it has been recognised that the adrenal glands are necessary for life, but knowledge of the functions of the intimately united cortex and medulla is still far from complete. It seems that the most vital functions are performed by the cortex, for Pende (1) showed, by destroying the adrenal medulla in a cat, that life could be maintained if the cortex were preserved.

The Adrenal Cortex

The presence of the adrenal cortex is essential for life. If it is removed the animal loses its appetite and its weight decreases rapidly. There is great muscular weakness, the basal metabolic rate is decreased, and body temperature and blood-pressure fall. Death results in the course of a few days. The chemical changes in the blood of such animals have been carefully studied and it has been found that the urea, non-protein nitrogen, potassium, and inorganic phosphorus are increased while the sodium chloride and bicarbonate and the sugar are decreased. The blood-volume is diminished and there is in consequence a relative polycythaemia. The low concentration of sodium chloride is

due to increased excretion by the kidney, and administration of sodium chloride and water will prolong life for considerable periods. If extracts of the cortex are administered regularly these changes will be prevented and the animal may live normally and even produce young. The symptoms observed in Addison's disease are in many respects similar to those caused by adrenalectomy in animals. There is no evidence of pigmentation in animals suffering from adrenal insufficiency and this may be due to some other factor, since the degree of pigmentation and the severity of the other symptoms in Addison's disease cannot always be correlated.

There has been much discussion among experimental physiologists as to the reason why animals fail to survive when deprived of adrenal cortical hormone (or hormones). Lock, Harrop, and their co-workers believe that the cortical hormone acts by influencing the kidney and that in its absence there is excessive renal secretion of sodium and water (2). Swingle, however, considers that there is a profound disturbance in the internal distribution of water and electrolytes and that capillary tone rather than kidney function is important (3). Zwemer *et al.* have noted the similarity between the symptoms of potassium poisoning and adrenal insufficiency, and the great toxicity of potassium when given to adrenalectomised animals (4). In cases of hyperfunction of the cortex it has been found that the level of the potassium of the blood falls and that it can be brought back to normal by the ingestion of potassium chloride (5). It is postulated that the adrenal cortical hormone enables the cell to retain potassium. Britton and his school maintain that interference with carbohydrate metabolism is of primary importance and that in adrenal insufficiency carbohydrate reserves are reduced to a level incompatible with life (6). Recently, however, it has been shown that there is an intimate relation between potassium and carbohydrate metabolism and it would seem that in adrenal insufficiency the changes in potassium metabolism are fundamental (7). Verzar has recently stated that the adrenal cortical hormone has an important influence on the process of phosphorylation (8). He believes that, in the absence of the cortex, dietary flavine

is not phosphorylated, which leads to avitaminosis B₂. Advances in this field are proceeding very rapidly and it is likely that the views of various workers will soon be correlated in an all-embracing theory.

There is considerable evidence to show that the adrenal cortex plays an important part in the normal resistance to infections, narcotics, and secondary shock. Adrenalectomised rats show a great decrease in their natural resistance to toxins, poisons, and infections and a disturbance in the capacity to form antibodies, while pathological studies also show cortical damage under similar circumstances. It is for these reasons and also because of the relative increase of blood potassium in acute infections and surgical shock that cortical extract is administered with encouraging results in patients suffering from diphtheria, exanthematous fevers, burns, and secondary shock (10) (21).

A cortical hormone was isolated in crystalline form by Reichstein and its chemical identity subsequently determined by the same worker (9). It has been called corticosterone. It is probable that other chemically related substances with a similar physiological action are also present in the adrenal cortex. A synthetic substance, desoxycorticosterone, derived from a sterol occurring in the soya bean, has been found to be more active physiologically than corticosterone itself and has proved very useful in treatment of Addison's disease.

The gonadotropic effects of the adrenal cortex are due to substances distinct from the life-maintaining principle. The presence of such substances was inferred from the appearance of masculinisation in females coincident with the growth of a cortical tumour, removal of which allowed refeminisation. When such tumours occur in the male before puberty, they cause pubertas praecox, usually accompanied by an increase in muscular development. The latter phenomenon may be due to the excess of male hormone. The same tumours in men may cause some increase in the size of the genital organs. Very rarely they may lead to feminisation (11) (12), so that it is possible that the hormone has a heterosexual function. The urinary excretion of male and female sex hormones is

considerably altered in conditions where sex reversal takes place, the males excreting more than the normal amount of oestrogens and the females more than the normal amount of androgens (13). A male sex hormone, androsterone, has been isolated from the cortex and crystallised, and Beall (14) has also obtained oestrone in crystalline form from adrenal extracts. A substance apparently identical with progesterone, normally derived from the corpus luteum, has lately been obtained from ox adrenal (15). Administration of cortical extracts to animals has shown that growth of the ovary and uterus may be produced (16) (17) (18) (19) and that masculinisation may be caused in females and genital atrophy prevented in male castrated animals (20).

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The Adrenal Medulla

The chromaffin cells of the medulla of the adrenal gland secrete adrenaline, the first hormone to be isolated and artificially synthesised. Its secretion seems to be governed by a centre in the floor of the fourth ventricle via the

splanchnic nerves and its effects are exerted upon the myoneural junctions, causing great sympathetic stimulation seen characteristically in Graves's disease. This sympathetic stimulation is countered by the inhibitory effects of the vagus and by substances that stimulate vagal action, notably ergotoxin, histamine, and choline. Adrenaline is not active when given by the mouth, but intravenous injection produces a rapid rise in blood-pressure and an increase in the heart rate; this effect is less rapidly produced by intramuscular and subcutaneous injections. The rise in blood-pressure is caused by stimulation and contraction of the arteriolar muscle, although not all arterioles react in the same way. The coronary, cerebral, and pulmonary arterioles and those of voluntary muscle undergo little contraction with sympathetic stimulation, whereas those of the intestines, liver, and kidneys contract with much greater intensity. The result is that there is a greater supply of blood to muscles and organs, which should be most active in circumstances of stress which call for rapid adjustment to surroundings and which normally provoke the sudden secretion of adrenaline. Many cases are on record in which an adrenal medullary tumour, usually a pheochromocytoma, has, by excessive secretion, produced hypertension with or without paroxysmal rises of blood-pressure, and sometimes accompanied by a great rise in the basal metabolism. The removal of these tumours has been followed by a relief of the symptoms (1).

Although adrenaline produces some stimulation of voluntary muscle, its main effect is on unstriated muscle. The tonus of the gastro-intestinal sphincters is increased, while the peristaltic movements of the gastro-intestinal tract are inhibited. This is well shown by the post-mortem examination of persons who have died in circumstances of prolonged severe anxiety, in whom it is found that a meal taken before the period of stress has not passed into the intestines after a lapse of some hours. The uterine muscle in human beings goes into tonic contraction under the action of adrenaline, but the bronchial musculature undergoes relaxation, a feature of which advantage is taken in treating bronchial

asthma. Intravenous injection of adrenaline causes contraction of the dilator fibres of the eye, of the unstriated fibres of the levator palpebrae superioris, and of the smooth muscle fibres at the back of the eye, so producing a condition similar to the exophthalmos seen in Graves's disease.

Varying effects are produced upon glandular organs. The secretion of sweat is not increased and the pancreas is inhibited but the activity of the salivary and gastric glands and of the liver is increased. A prolonged diuretic effect is exercised upon the kidneys. Adrenaline exerts its effect upon carbohydrate metabolism by causing the rapid conversion of glycogen into glucose. The glycogen is mainly derived from the liver and it has been noted that loss of muscle glycogen occurs only in the starved animal. The glucose thus freed causes a rise in the blood-sugar which increases for about two hours and then falls slowly (2). With the rise in blood-sugar above the kidney threshold, glycosuria occurs and persists as long as adrenaline is in circulation and the glycogen stores are not severely depleted.

Physiological Interrelationships of the Adrenal Glands

The adrenal glands depend upon the anterior lobe of the pituitary gland for their growth and function. It is therefore to be expected that alteration in adrenal function should be accompanied by changes in the pituitary and vice versa. That such is the case is shown by the coincident abnormalities of the pituitary and atrophy of the adrenal cortex in anencephalic foetuses (3) and by the reduction in the size of the cortex which follows the atrophy of the pituitary in Simmonds's disease. Degeneration occurring in the adrenal cortex is followed by a decrease in the number of the basophil cells of the pituitary (4).

The secretions of the posterior lobe of the pituitary gland act in relation to the adrenal cortical and medullary hormones. The salt and water metabolism regulator of the cortex acts synergically with the antidiuretic factor of the posterior pituitary lobe, and the polyuria and intestinal

paresis caused by adrenaline sympathetic stimulation are relieved by the same hormone (pitressin).

The influence of insulin on the ability to store carbohydrates is antagonised by the adrenal cortical and medullary hormones alike. The severe diabetes of a pancreatectomised dog is relieved by the removal of the adrenal cortex and restored by the subsequent injection of cortical extracts (5) (6). An effect contrary to that of insulin is also seen in the cortical regulation of fat metabolism, for insulin apparently prevents ketosis and the adrenal cortical hormone stimulates it (5).

The fall in the blood-sugar caused by the injection of insulin stimulates the production of adrenaline which causes glucose to be set free from the liver. Clinically, adrenaline is used to remedy the hypoglycaemia which is the cause of insulin shock.

A relation between the gonads and the adrenal cortex is now well established. Excessive cortical activity will, in the case of women, cause the growth of a beard and moustache, accompanied by an increase of androgen excretion (7), and the androgens present in cortical tumours may cause sexual precocity in males and virilism in females. The recent discovery of the presence of oestrogens in cortical tissue shows also how feminine characteristics may occasionally be produced in cases of cortical tumours in men. Furthermore, a substance apparently identical with progesterone has been isolated from adrenal cortex (8), and its excretion product, sodium pregnanediolglycuronide, may be found in large excess in virilism due to a cortical tumour (9). Desoxycorticosterone is structurally similar to progesterone and its progesterone-like action has been used experimentally to prevent the formation of "fibroid" uterine tumours which result from prolonged administration of oestrogens (10).

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The Thyroid Gland

The thyroid gland owes its physiological activity to thyroglobulin, an iodine-containing compound found in the colloid material secreted by the epithelial cells lining the vesicles of the gland. The active chemical constituent of thyroglobulin is thyroxine (1), a tyrosine compound containing 65 per cent of iodine which was synthesised by Harington and Barger (2). The thyroid hormone is present in its highest concentration in the thyroid gland but has been found in nearly all body tissues and in the body fluids. In the blood, 60 per cent of the iodine is alcohol-insoluble (thyroxine) and 40 per cent alcohol-soluble, but this balance is disturbed in thyroid disease; in hyperthyroidism, there is a relative increase in the alcohol-insoluble fraction and the administration of Lugol's iodine (alcohol-soluble) ameliorates the condition temporarily, probably by restoring the balance; in myxoedema, on the other hand, the alcohol-insoluble fraction is lowered very considerably. For clinical purposes these variations are useful for comparison with the basal metabolic rate, because the blood-iodine concentration runs nearly parallel with the basal metabolic rate.

The most important function of the thyroid hormone is its effect on metabolism, which is evaluated by determining the basal metabolic rate. This is a measure of the speed of the chemical changes taking place when the body is at its lowest level of activity, and is estimated by the rate of consumption of oxygen. It is increased by excess of the thyroid hormone which brings about rapid combustion of the carbohydrates, proteins, and fats, speeds up the heart and respiration, increases water excretion through the kidneys, stimulates muscle activity, increases the irritability of the nervous system, and makes the individual bright and intelligent. Attention has, however, recently been drawn to the fact

that the symptoms of increased thyroid activity caused by hyperplasia of the gland are not invariably accompanied by a raised basal metabolic rate (3).

The quickened metabolism of the hyperthyroid patient causes a rapid destruction of the liver glycogen and the blood-sugar in the glucose tolerance test rises rapidly above the renal threshold and returns to normal within one and a half hours. Glycosuria may sometimes be observed but the fasting blood-sugar is usually normal. The rapid rise in the blood-sugar curve is stated by Althausen (26) to be due to an increased rate of absorption of glucose by the gut. The metabolism of the body proteins, particularly that of the muscles, is increased in hyperthyroidism, as shown by the increase in the excretion of urea and creatine. One of the responses of the myxoedematous patient to thyroid medication is that creatine, usually absent in the urine of such cases, once more makes its appearance.

The metabolism of water and sodium chloride is altered by excess or lack of thyroid. With thyroid lack, as in myxoedema, water is retained in the tissues and the volume of the plasma is low, but when thyroid hormone is given, water and salt are excreted by the skin and kidneys, the plasma volume rises, and the dry, cool thick skin returns to normal.

The effect of the thyroid hormone upon fat metabolism is well seen in the hyperthyroid patient, in whom the decrease of body fat is obvious. The blood cholesterol in thyroid imbalance varies inversely with the basal metabolic rate, falling in hyperthyroidism and rising steadily in myxoedema, increasing up to four times the normal figure in severe cases.

An alteration in calcium metabolism, varying with the amount of thyroid hormone produced, is evident on comparing the osteoporosis of the hyperthyroid patient with the increased density of the bones in hypothyroid states. About 50 per cent of hyperthyroid patients show a rarefaction of the skeleton and excrete an excess of calcium and phosphorus in the faeces, while the opposite state occurs when there is lack of thyroid hormone.

The raised temperature of the hyperthyroid state is a further consequence of the increased rate of metabolism; for example, the administration of thyroxin to a hibernating ground squirrel causes a rapid rise in body temperature and an awakening out of its winter sleep (4).

The growth and development of the tissues is influenced by the thyroid hormone, and these are particularly well observed in the lower vertebrates, as was shown by Guder-natsch (5), who found that the metamorphosis of tadpoles was speeded up by giving thyroid. Slow somatic growth, mental and sexual development are clinical features of the result of lack of thyroid in human beings. The bone age is retarded if the disease has been present for any length of time, and in some cases the epiphyses may show a stippled or fragmented appearance resembling bilateral Perthes's disease (6). On the contrary, the early appearance of the centres of ossification may be a feature of hyperthyroidism in childhood (7). The presence of excess of thyroid does not necessarily lead to an acceleration in bone growth, for Bloom (8) noted that there was a general retardation of growth in length of bone in hyperthyroid children, and this was confirmed experimentally by Smith and McLean (9), who found that the feeding of thyroid to rats led to premature ossification or retardation of growth of the long bones by endochondral bone formation, possibly preceded by a period of stimulation of growth.

The action of thyroxin is strongly inhibited by inorganic iodine, which has long been used for prolonged treatment and more recently for pre-operative therapy. Quinine, too, acts antagonistically to thyroxin and is used clinically with favourable results in hyperthyroid patients, who can tolerate large doses without experiencing cinchonism.

There is a relationship between thyroid activity and vitamins A, B₁, and C. Large quantities of vitamin A will prevent the loss of weight which is caused by thyroxin. This has been found to be true in rats (10), thyroidectomised guinea-pigs (11), and in human beings (12). Other observers (13) have found that large amounts of vitamin A, when given to rats, will counteract the effect of thyroxin on the basal

metabolic rate and weight. An adequate supply of thyroxin is necessary to enable the liver to convert the carotene of the food into vitamin A (27). Deficiency of vitamin B₁ is stated by Motila (14) to result in atrophy of the thyroid. As a result of the administration of thyroxin to rats the liver loses part of its vitamin B₁ (15), but if vitamin B₁ is supplied in sufficient amount to the animals the effects of thyroxin are largely nullified (16). In several recent articles (17) it is reported that vitamin C is rapidly exhausted in hyperthyroidism and clinical evidence of this has been furnished by the use of urinary estimations of ascorbic acid. For example, of five hyperthyroid patients who were thyroidectomised, four showed a return to the normal excretory values of ascorbic acid after operation and the fifth showed increased excretion (18). It has been established (19) that the administration of vitamin B₁ prevents the depletion of the tissue reserves of vitamin C caused by thyroxin in rats, thus showing relationship between the vitamins.

The relation between the anterior lobe of the pituitary and the thyroid gland has been discussed in the section on anterior pituitary hormones. It is sufficient here to recall the underlying principles. The anterior pituitary lobe stimulates secretion of the thyroid gland by means of the thyrotropic hormone. As a consequence of lowering of pituitary function there is a decrease in activity of the thyroid. Conversely, if the thyroid shows an extreme diminution of its function, as in cretinism, a compensatory effort is made by the anterior pituitary lobe, which undergoes enlargement in order to produce more thyrotropic hormone. An antagonism exists between the posterior lobe of the pituitary and the thyroid. Mahoney and Sheehan (20) showed that experimental diabetes insipidus produced in dogs could be abolished by subsequent thyroidectomy and that the symptoms returned on administration of thyroid. They were able to induce extreme polyuria and oliguria by giving or withholding desiccated thyroid. This suggests that the antidiuretic hormone of the posterior pituitary lobe is countered by the diuretic properties of thyroxin.

Adrenaline, the hormone of the adrenal medulla, acts in

synergism with the thyroid, for it is the main activator of the sympathetic nervous system and therefore speeds up the functions of the thyroid which is entirely supplied by sympathetic nerve fibres.

There is a close relationship between the thyroid and gonadal activity. The thyroid may swell during menstruation, and the onset of puberty or the advent of pregnancy may determine thyroid enlargement, especially if there is any lack of iodine. The effects of thyroidectomy upon the gonads vary with the species of animal; in dogs (21) no histological changes have been found in the testes or ovaries; ground squirrels (22) show an infantile condition as regards spermatogenesis and hormone production, and hens exhibit a remarkable drop in egg-production which can be restored to normal by giving thyroxin (23).

A relation also exists between the thymus and the thyroid, for both glands may be enlarged in Graves's disease, the thymus is frequently enlarged in cretinism, and an atrophic thymus may be regenerated by the administration of thyroid.

The increase in the breakdown of protein which follows the administration of thyroid gland is to some extent offset by the adrenal cortex. Zwemer (24) found that animals which had been adrenalectomised, survived longer if the thyroid had also been removed. Other observers (25) subsequently showed that the protein loss caused by giving thyroxin to an adrenalectomised animal could be lessened or even converted into a gain of protein by administering suitable amounts of cortical hormone.

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The Parathyroid Glands

The physiology of the parathyroid glands is so intimately connected with the metabolism of calcium that some knowledge of the latter is essential.

Calcium metabolism is influenced by four principal factors: (1) sufficient intake; (2) presence of vitamin D; (3) hydrogen ion concentration in the intestine and blood; (4) parathyroid hormone. The calcium requirement of the body varies with the age, about 1 gramme per day (1) being essential in the early days of life when the body is rapidly building up a skeletal framework, and about 0.5 gramme daily in adult life. Pregnancy and lactation cause a rapid increase in the maternal requirements, for the foetus absorbs two-thirds of its calcium in the last two months of intra-uterine life, and after parturition the secretion of calcium in the milk is a constant drain upon the resources of the body.

Vitamin D is essential for the utilisation of calcium and phosphorus in correct proportions. It is formed by the action of ultra-violet light upon the ergosterol^{*} present in the skin, the amount formed being inversely proportional to the degree of pigmentation of the skin, so that dark-skinned races are more likely than white people to suffer from lack of this vitamin, given the same amount of light. However, failure of absorption from the skin can be compensated by suitable food or administration of the vitamin itself. Thera-

peutic dosage with vitamin D is followed by increased calcium absorption only in cases where there is a deficiency, and in normal people any excess of calcium or phosphorus ingested is soon excreted.

The absorption of calcium takes place in the upper part of the small intestine and takes place most easily when the intestinal contents are acid. The presence of excess of fatty acids, as in coeliac disease, interferes with the absorption of calcium, so that osteoporosis is likely to occur. Phosphatase enzymes present in the intestinal mucosa facilitate the absorption of calcium and phosphorus by splitting the phosphorus esters in the food and forming soluble inorganic salts. Phosphatase is present in the blood and its quantity is greater in growing children, who are forming new bone tissue, and in certain conditions which are accompanied by bone absorption. The normal blood-level of calcium is 9 to 11 mg. per 100 c.cm.; this is wholly in the plasma, which is supersaturated, and none is present in the corpuscles. About half the total calcium in the serum is non-diffusible through the capillary membrane, and it is doubtful whether it has much physiological activity; the remainder is diffusible and part of it is in ionised form and active physiologically. Calcium is necessary for a number of purposes. By means of bone phosphatase formed in the osteoclasts, a complex calcium phosphate is laid down in osteoid tissue, converting it into bone: the excitability of muscles and nerves is greatly increased if the serum calcium is decreased and there is a liability to the development of tetany: an essential part is played in the clotting of blood and ingested milk: the permeability of the capillaries is diminished by calcium and such allergic phenomena as urticaria, asthma, and serum rashes are inhibited.

The hormone of the parathyroid glands, named parathormone by Collip, is only active when given parenterally. Subcutaneous or muscular injection leads to a mobilisation of the calcium in the bones, with a rise in the serum calcium, a decrease in the phosphorus, and an increase in the excretion of calcium and phosphorus. Large doses of the hormone produce diuresis with rapid demineralisation of the body;

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finally, the kidneys become affected by metastatic calcification and anuria; bloody diarrhoea and death in uraemic coma ensue. Large doses given over a long period cause decalcification of the skeleton, the bones being replaced in part by fibrous tissue or by giant-cell tumours and the calcium which is set free is deposited in various organs. Continuance of administration may sometimes lead to a state of immunity which is caused by the formation of an antihormone. Selye (1) found in experiments on rats that the prolonged administration of large doses of parathyroid extract was at first followed by skeletal decalcification and replacement of bone by fibrous tissue, but continuance of dosage produced immunity and sometimes the deposition of bone in such density that the final condition resembled "marble-bone disease". It is interesting to note that in one instance (2) a parathyroid tumour has been found associated with marble-bone disease, which suggests the possibility that chronic hyperparathyroidism may have caused an immunity and subsequent production of hypercalcification.

The method of action of parathormone is not fully understood; Collip believes that it acts by stimulating the osteoclasts, which release calcium from combination, enabling it to enter the blood in ionised form. Parathyroid insufficiency, caused by disease or by accidental removal in thyroidectomy, causes a fall in the serum calcium and a retention of inorganic phosphorus in the blood. When the serum calcium is down to 6 to 8 mg. per cent the muscle and nerve irritability is increased to such an extent that stimulation of a motor nerve is followed by prolonged muscular spasm, and at levels of 4 to 6 mg. per cent the symptoms of manifest tetany develop. Chronic hypoparathyroidism is likely to be accompanied by defective bone growth and osteoporosis, with slow healing of fractures: cataracts are common, the hair may fall out, the nails become brittle, and the teeth develop defects in the enamel.

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The Thymus

The exact part played by the thymus in endocrine physiology has still to be determined, for up to the present the results of experiment have been contradictory.

Asher and his co-workers (1) have stated that injections of a thymus extract called thymocrescin produced rapid growth and sexual maturation in rats, but other investigators (2) have been unable to confirm these results either in the first or succeeding generations of rats. Rowntree and his fellow workers (3) claimed that, by continuous intraperitoneal injections of thymic extract into successive generations of rats, rapid acceleration of growth and adolescence were produced, with an increase in the blood calcium and phosphorus and early calcification and union of the epiphyses. The rate of growth was speeded up to about ten times the normal, teeth and hair appeared at a proportional speed, and mental precocity was similarly advanced. It was also noted that the fertility of these rats was increased. These effects upon the growth of the animals were only temporary, so that gigantism did not occur and the normal control rats caught up to the experimental animals after sixty days. They also found that thymectomy in successive generations caused a retardation of growth which could be prevented by daily intraperitoneal injections of Hanson's thymic extract (3). Although the hormone responsible was not known, it was claimed that certain iodine-reducing substances found in the thymus were the partial causes of the growth and development (5). Injections of this extract are also stated to bring about a rapid myelination of the central nervous system (6). Confirmation of the results obtained by the Asher and Rowntree groups has not yet been published.

Adler (7) suggests the further possibility that the thymic secretion is responsible for the excessive destruction of acetylcholine in myasthenia gravis. By means of thymus implants and injections of thymic extracts in dogs, he caused a severe myasthenic reaction: this condition, similar to myasthenia gravis in human beings, was rapidly relieved by

the administration of eserine, which has the effect of preventing the rapid destruction of acetylcholine at the neuromuscular junction. In this connection it is interesting to note that thymic enlargement occurs in 90 per cent of cases of myasthenia gravis.

There is a relationship between the sex hormones, whether secreted by the gonads or adrenals, and the thymus. Removal of the adrenals in mice (9) and dogs (10) has led to the enlargement of the thymus and lymph glands, and in Addison's disease, a similar condition clinically, hyperplasia of the thymus is frequently noted. A decrease in the hormonal functions of the gonads is associated with thymic hyperplasia, as is seen in cases of hypogonadism, while gonadal over-function, as simulated experimentally in mice by treatment with oestradiol, is responsible for thymic atrophy. Prolonged treatment with oestradiol in these animals leads to the formation of lymphosarcomata, usually starting in the thymus (8).

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The Pineal Gland

Experimental and clinical evidence regarding any hormonal function of the pineal gland have yielded such conflicting results that it is not possible to form any conclusion. The most suggestive experimental results have been afforded by Rowntree's (1) observations on successive generations of rats which were given intraperitoneal injections of pineal extract. The treated animals showed dwarfism, with sexual

precocity and some genital enlargement. This is in accord with the clinical observation that macrogenitosomia praecox may follow the development of tumours of the pineal gland. Rowntree's results, however, have not yet been confirmed by other investigators. It is possible that the gonadotropic hormone of the pituitary may be stimulated either directly or indirectly through the hypothalamus (2).

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The Pancreas

Insulin, the internal secretion of the pancreas, is produced by the beta-cells of the islets of Langerhans. Active extracts of insulin were first obtained by Banting and Best in 1922 and the hormone was prepared in crystalline form by Abel in 1926.

Failure in the adequate production of insulin is responsible for pancreatic diabetes, a condition which is characterised by the presence of an inordinate amount of sugar in the blood. The high blood-sugar of the diabetic has been accounted for in two ways which can briefly be described as the theories of "under-consumption" and "over-production" of glucose respectively. The "under-consumption" theory is supported by the fact that most of the tissues of the diabetic animal, except the brain, show a reduced capacity for the oxidation of glucose. The theory of "over-production" receives support from the fact that the diabetic on a carbohydrate-free diet still produces large amounts of glucose while the liver and muscle glycogen remain low. The injection of insulin causes a fall in blood-sugar accompanied by a rise in the glycogen content both of liver and of muscle. If the position is stated in this way it is evident that the theories are not necessarily incompatible with one another.

It has been estimated (1) that the normal insulin requirements of the body are 0.005 unit per kg. body weight per hour (or roughly 30 units per day). Its utilisation is so rapid

and the physiological needs of the body vary so continually that it has been necessary to find a substance which will remedy the frequent oscillations of blood-sugar in diabetic patients and approximate to the natural flow of production. To meet this demand, protamine zinc insulin was produced. Its solution is so slow that the effect only begins to be apparent after about nine hours and may sometimes be detectable thirty hours after injection.

Failure in insulin production also has an effect upon the metabolism of fats, which are incompletely oxidised and appear in the blood and urine as ketone bodies ; at the same time the blood fat and cholesterol are increased.

The effect of insulin upon the metabolism of carbohydrates is modified by hormones secreted by the pituitary, adrenal, and thyroid glands.

The anterior lobe of the pituitary is known to form a diabetogenic hormone antagonistic to insulin, for injections of the anterior lobe will induce permanent diabetes in dogs with the production of hydropic degeneration in the beta-cells and a low insulin content of the pancreas (2). This effect is suggested clinically by the observation that hyperglycaemia may be present in acromegalics and that hypoglycaemia is a notable feature following the pituitary atrophy of Simmonds's disease. The oxytocic fraction of the secretion of the posterior lobe of the pituitary gland is also antagonistic to insulin and causes a hyperglycaemia if the liver is not exhausted of its glycogen.

Adrenaline opposes the effect of insulin by causing the mobilisation of glycogen at first from the liver and later from the muscles. It is used clinically to cause a rapid rise of the blood-sugar in attacks of hypoglycaemia. Extract of the adrenal cortex also causes a rise in the blood-sugar and will remedy the hypoglycaemia of Addison's disease.

One of the effects of thyroxin is to cause mobilisation of the hepatic glycogen, and it is frequently found that thyrotoxic patients exhibit a temporary hyperglycaemia and glycosuria after a meal. According to Althausen (7), this hyperglycaemia is probably due to an increased rate of gastro-intestinal absorption of carbohydrate. If a diabetic

patient develops hyperthyroidism, the carbohydrate tolerance is lowered still further, and conversely, when myxoedema and diabetes are present together, the diabetic condition is favourably influenced (3).

In the liver, the breaking-down of glycogen by a glycogenase which is normally present is facilitated by the action of bile salts ; in fact, the accumulation of bile salts in obstructive jaundice may be so great as to prevent the formation of glycogen from the blood-sugar for a while and so cause a temporary hyperglycaemia (4). Exteriorisation of the bile-duct has even been used for " surgical " cure of diabetes.

The utilisation of insulin may be aided by ascorbic acid, as it is claimed that diabetics need smaller doses of insulin to control their symptoms if ascorbic acid is given as well (5).

Hyperfunction of islet tissue, due to adenoma and carcinoma of the Langerhans cells, leads to a low blood-sugar, attacks of hunger, faintness, mental symptoms, and convulsions. It is to be noted that hypoglycaemia occurs regularly in the new-born, lasting for about four days, and is possibly due to hormonal imbalance with a preponderance of insulin : this condition is of particular importance in the case of children who are the offspring of diabetic mothers ; they are often large at birth and may suffer so severely from hyperinsulinism that a fatal termination is likely (6).

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Hormone Interrelationships

The growth and functions of the ovaries depend on the secretions of the pituitary gonadotropic hormones in the right proportions at the proper time. Similarly, the secre-

tion of the male hormone and the production of spermatozoa are controlled by the pituitary. The male and female gonads produce not only the hormone which maintains their own secondary sex characteristics but that of the opposite sex as well (1) (2). Consequently, the metabolic products of testosterone are found in the urine of females and those of oestradiol in males. In gynecomastia the excretion of oestrogen is relatively high and in some cases a testicular tumour may lead to over-production of female hormone. Prostatic hypertrophy may be induced in animals by oestrone, which acts on the middle lobe and by testosterone, which increases the proportion of glandular tissue (9). This has led some people to attribute prostatic hypertrophy in old men either to excessive secretion of oestrogens by the testis, or else to the presence of a relative increase in oestrogens, which is due to the diminished secretion of androgens in senility. These hypotheses are the basis for the treatment of senile prostatic hypertrophy with testosterone.

The adrenals also produce sex hormones, and this probably accounts for the small amounts of these substances excreted by male and female castrates, while the enlargement of the adrenals observed after castration may be a compensatory hypertrophy. Symptoms of virilism observed in women and associated with adrenal tumour are similar to the masculinisation effects produced in female monkeys by giving male hormone. Cases of feminisation in males with adrenal tumours have also been recorded and these have been associated with a considerable excess of secretion of oestrogenic hormone (10).

It has not been shown that the sex hormone of the opposite sex plays any particular part in the sexual make-up of either males or females, although its presence may be made manifest if for any reason the balance between the hormones is disturbed in favour of that of the opposite sex. Both male and female hormones have a certain amount of bisexuality, i.e. oestrogens will cause growth of the seminal vesicles and prostate of a castrated male mouse (3) and androgens have a similar effect on the uterus and vagina of a spayed female mouse (4). Substances related to testosterone

have been synthesised which possess both oestrogenic and progestational as well as androgenic activity.

Intersexuality has been produced both in birds and mammals by treatment of embryos *in utero* or of young animals with sex hormones. Willier *et al.* (5) have obtained masculinisation of female chick embryos by treatment with testosterone during incubation, while Greene *et al.* (6) (7) (8), working with rats, have produced masculinised females and feminised males by administration of androgens and oestrogens to pregnant animals. The masculinised genetic females have uteri, oviducts, and the upper part of the vagina and also epididymis, vas deferens, seminal vesicles, ejaculatory ducts, prostatic lobes, Cowper's gland, and penis. The feminised males possess mamillae and a vagina while the development of the male genitals is considerably reduced. Antenatal treatment of mammals with oestrogens generally leads to abortion, but this can be avoided by the use of oestradiol dipropionate which is absorbed very slowly, and diethylstilboestrol has similar effects.

Considerable doses of gonadal hormones lower the activity of the gonads, probably through an inhibitory effect on the pituitary. The effects of the administration of testosterone propionate in female animals vary according to the dosage employed and the length of treatment. Given to immature female rats, minimal amounts cause ovarian stimulation, while more vigorous treatment will produce temporary degenerative changes and inhibition of function, in addition to a decrease in the weight of the pituitary and adrenals and mucification of the vaginal epithelium (11). When given to rhesus monkeys, male hormone inhibits ovarian follicular growth and luteinisation and stops menstruation. When given to women in doses varying between 30 and 120 mg. during one month, sufficient effect is produced to prevent metrorrhagia without disturbing the normal menstrual rhythm (12), and larger doses (450–1000 mg. during thirty days) will inhibit secretion of the ovarian hormones and, in consequence, ovulation and menstruation, with resulting loss of fertility (13). Changes similar to the latter can be produced by large dosage with oestradiol, and it must be



remembered that the male hormone, if used in excess, may cause facial hair and masculinisation of the voice (12). The general depression of pituitary function which is caused by administration of testosterone propionate can be used in the rapid suppression of lactation. Like oestradiol, testosterone will relieve menopausal symptoms and it has the advantage of not stimulating the endometrium to proliferation (14). A further possible use is its employment for preventing the formation of thyrotropic hormone in Graves's disease.

Administration of excess of oestrogenic hormone to male or female mice causes hyperplasia of the anterior lobe of the pituitary largely due to an unusual amount of chromophobe cells (15). Functionally, this is associated with a general condition of hypopituitarism. These anterior lobe changes do not occur if thyrotropic hormone is given simultaneously with the oestrin, suggesting that these two hormones act antagonistically (16). Further evidence of this antagonistic action is the fact that thyrotropic hormone, when given to male mice treated with oestradiol, will prevent the hypertrophy of the breast tissues which normally follows the administration of large doses of the female hormone: it is possible, too, that the small resting thyroid found in mice treated with oestradiol is a result of this hormonal opposition. In human beings the amounts of oestradiol which are given clinically are small in comparison with those given in animal experiments and are unlikely to produce severe results. Rowlands and Sharpey-Schafer (18) found no gross enlargement of the human pituitary gland in patients who were given oestradiol benzoate in quantity sufficient to abolish the presence of a gonadotropic substance in the urine and to cause considerable diminution in the gonadotropic activity of the pituitary.

A close connection exists between the adrenals and the ovaries: excessive supply of the ovarian hormone will counteract to some extent the loss of the adrenal hormone which is necessary to life, and will, in the unadrenalectomised animal, cause brown atrophy of the adrenals. Treatment with oestradiol is also found to cause rapid atrophy of the testis in mice, but this change is much less if the adrenals

have previously been removed. These experimental results suggest that one of the hormonal functions of the adrenal acts synergically with oestradiol (17).

A relationship exists between the thymus and the gonads. If castration is performed at an early age or if the functional activity of the gonads is considerably reduced, the thymus fails to undergo its normal involution, and on the other hand the thymus undergoes atrophy in mice which have had an experimental hypergonadism induced by treatment with oestradiol (17).

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CHAPTER 3

METHODS OF EXAMINATION

Physical Examination

Anthropometry

NON-ENDOCRINE disease having been excluded, the patient undergoes general and regional examinations to ascertain glandular dysfunction. Of these, the first and most important is a routine set of measurements which will establish deviations from the maximal and minimal normal anatomical variations. For this purpose we have used the carefully compiled tables published by Engelbach which have as their basis the examination of over two and a half million native-born whites of the U.S.A. by forty different authorities. The measurements thus obtained were compared with those of a large number of persons free from endocrine imbalance and in whom the roentgenological evidence of osseous development was normal. Preference has been given to these tables because the maximal and minimal variations from the normal mean value are sufficiently wide to include the increases in stature and weight which have been noticed in recent years, and because, unlike many other tables, they have been drawn up with the specific object of differentiating types of endocrine disease and therefore contain the necessary data. See table, p. 290. The measurements to be taken are :

- | | |
|------------------------------|-----------------------|
| (1) Circumference of head | (5) Height |
| (2) Circumference of chest | (6) Lower measurement |
| (3) Circumference of abdomen | (7) Upper measurement |
| (4) Span | (8) Weight |

The circumference of the head is taken just above the eyebrows ; the circumference of the chest is taken at nipple-level in the male and at the level of the fourth interspace in

women ; the circumference of the abdomen is taken at the umbilical level in the male and approximately at the same place in females with pendulous abdomens. Any other regional measurements, such as round the thighs or pelvis, are to be taken at a known distance from bony points so that subsequent changes may be properly compared. The lower measurement is the distance from the top of the pubic bone to the sole of the foot, and by subtracting this measurement from the height one obtains the upper measurement, which is the distance between the top of the pubic bone and the crown of the head. The span is the distance from the end of one middle finger to the other when the arms are stretched laterally at right angles to the body with the palms facing forwards, and is obtained by doubling the measurement from the tip of one middle finger to the middle of the manubrium. It will be noticed that increases in the lower measurement and the span are largely due to development in the long bones and that changes in the upper measurement are due to short-bone growth.

Skeletal Growth

At birth, the upper measurement is much longer than the lower, but rapid increase in the long bones results in the two measurements becoming equal at about the age of 12 ; thenceforward, the lower measurement slightly exceeds the upper in the male and both are approximately the same length in the female. The span equals the height at about 10 years of age and thereafter exceeds it by about an inch. Skeletal growth takes place in two ways—at the ends of the diaphyses of the long bones and subperiosteally in the case of the short and flat bones. As diaphyseal is more rapid than subperiosteal growth, any factor accelerating growth will cause relative increase in the length of the long bones, and conversely, a relative diminution in the length of the long bones is usually caused by lack of, or inhibition of, the growth hormone. The principal factors concerned in bone growth are the hormones furnished by the pituitary and thyroid glands, the gonads and possibly the adrenal cortex. If the growth hormone of the pituitary gland is deficient, as occurs

in hypopituitarism, its failure will be particularly evident in the long bones, which remain disproportionately short so that the individual retains the statural proportions of a child of under 12 years of age, but if the hormone is present in excess or is unchecked in its effects, long-bone growth becomes excessive and undue tallness results. Lack of thyroxin manifests itself in the late appearance of the centres of ossification and a slowing-up of the growth of the skeleton, while thyroid hyperactivity results in an early appearance of osseous centres or the presence of a greater number than is normal for the age ; increased growth is also present when the thyroid is over-active. One of the effects of the gonadal hormones and possibly of the adrenal cortical hormone is the inhibition of the growth factor and the promotion of closure of the epiphyseal lines, so that patients in whom these factors are deficient will continue to grow in height and may fail to obtain epiphyseal fusion. In hypergonadism or hyperadrenalism, excess of these factors will, in addition to producing premature puberty, cause an early epiphyseal closure and consequent dwarfism.

It must be remembered that disorders of internal glandular secretion are not limited to any one gland and that the secondary effects of the dysfunction may disguise the source of the trouble ; for example, a late result of pituitary infantilism is the failure of gonadal development, which, in its turn, results in lack of secretion of the anti-growth factor, so that continued slow bone growth may persist, thus altering the proportions usually found in that disorder.

Weight

Alterations of body weight are due mainly to muscular development or obesity, both of which are largely under the control of the pituitary and thyroid glands and the gonads. The muscles are big in pituitary hyperfunction and hypergonadism and small in the corresponding hypofunctions. Lack of physical strength and ready exhaustion are signs present in hypo-adrenalism and hyperthyroidism. The obesity in childhood pituitary obesity is of feminine distribution ; the increased size of the breasts is due to a layer of

fat and not to glandular tissue and there is also a heavy covering of fat over the abdomen, the pubes, and the proximal parts of the arms and legs. In hypothyroidism the distribution is more general, with accumulations above the clavicles and around the wrists and ankles. Thinness is typical of the cachexia in Simmonds's disease and is also met with characteristically in hyperthyroidism and primary hypogonadism of the male or female ; in late hypogonadism, however, fat is deposited around the pelvic girdle.

Regional Examination

In examining the head, attention is directed to its size and shape, the closure of the sutures, and the facial expression. Any advance or delay in the dental age is determined by inspection of the erupted teeth and by radiography. Eruption is delayed in hypothyroidism and the subsequent irregular appearance of the second dentition leads to overcrowding. In hyperpituitarism and hyperthyroidism eruption is advanced. The teeth share in the general lack of somatic growth in hypopituitarism and are small and widely spaced. The lateral incisors are typically stunted in hypogonadism and the teeth are crowded owing to the smallness of the jaws. The patient should be encouraged to speak in order to detect any abnormalities of speech or undue alteration in the pitch of the voice. The eyes are tested for any defect in vision and the fundus is inspected for changes in the optic disc or alterations in pigmentation, while the visual fields are examined if there is any possibility of an intracranial tumour.

Any tumour of the thyroid should be measured for future comparison at the level of maximum circumference and it should be noted when the patient is swallowing whether any portion of the tumour rises out of the thorax.

The chest may show an unusual hairiness, or hairs round the nipple may be associated with a masculine distribution of the abdominal hair in the female. The breasts in females may be largely composed of fat and the nipples tiny in childhood pituitary obesity, or in other conditions

the breast tissue may be in disproportion to the size of the nipple, suggesting an abnormal balance of ovarian secretions. As endocrine diseases so frequently cause alterations in metabolism, it is only to be expected that these should be reflected in the circulatory and respiratory mechanisms. The pulse is quickened in hyperthyroidism and slowed in hypothyroidism and the asthenic conditions of hypopituitarism and hypo-adrenalism. The respiration is speeded up with increased metabolism; cough or stridor may be caused by intrathoracic tumours of the thymus or thyroid.

Skin

The presence of a fine downy hair on the body should be noted, as also the presence or absence of hair in the axillae and over the pubes and its distribution according to the sex. A general hairiness is noted in adrenal over-function. Axillary and pubic hair may be lacking in under-function of the pituitary and gonads and appear early in hyperfunction of these glands. A heterosexual distribution of hair is evidence of gonadal dysfunction. The hair on the head is fine and silky in hyperthyroidism, coarse and scanty in hypothyroidism, where also the outer third of the eyebrows may be lacking. The texture of the skin is frequently altered in endocrinopathies, and pigmentations or eruptions may be present. A thin, smooth skin with a high-coloured complexion is found in childhood pituitary obesity while in hypopituitarism (growth deficiency) there is wrinkling and general sallowness. In Graves's disease the skin is moist, warm, and thin, and in hypothyroidism it is dry, cool, and thick. Acne is common in hypogonadism, and also at adolescence and at about the time of the menstrual periods. Patients with hypogonadism also have a sallow complexion.

The skin over the lower part of the abdomen frequently shows striae in cases of obesity, these being especially marked in pituitary basophilism. The child may be pot-bellied in cretinism or the abdomen pendulous in childhood pituitary obesity. Palpation in the erect posture may show evidence of visceroptosis, which is associated with the lax musculature in hypogonadism and hyperthyroidism.

Limbs

Examination of the limbs may disclose excessive length or shortness ; the fingers may be long in gigantism and hypogonadism, tapering in hypopituitarism, or short and stubby in cretinism and hypergonadism.

Genital Organs

Examination of the genital organs may reveal precocious development accompanied by early libido and emissions, and the appearance of the secondary sexual characteristics or an early onset of menstruation in the female ; such conditions may be caused by over-activity of the pituitary gland or gonads and more rarely by abnormal secretion of the adrenal cortex. In association with diminution of the pituitary or gonadal hormones, puberty may be retarded and the genital organs may remain in an undeveloped condition ; furthermore, the psychological attitude which is proper to the age of the individual may show a corresponding failure of development. In females, estimation of genital development is more difficult, with the result that the child is not usually brought for examination unless there has been some abnormality of menstruation. For details of methods of examination of the adolescent female see Chapter 8.

Radiographic Examination

Endocrine imbalance during childhood and adolescence very frequently results in changes in the formation of bone and the rate of growth, so that radiological evidence of abnormalities in the appearance of the centres of ossification or in the time of fusion of the epiphyses is of great importance in the diagnosis. Delay in the appearance of the ossific centres is characteristic of under-function of the thyroid gland ; hence, if there is considerable delay of the osseous as compared with the chronological age of the patient, one is safe in assuming under-activity of the gland. This observation is so easily made that it should always be undertaken in the case of a child who is over-weight at birth. A decrease in the density of bone tissue is noticed in cases of hyperthyroidism

and notably in hyperparathyroidism, in which latter disease it may be so severe as to cause spontaneous fractures. Thin, slender bones occur in patients suffering from hypopituitarism and hypogonadism.

The length of the long bones, provided that the thyroid is normal, is controlled by the growth hormone of the pituitary gland and the secretion of the gonadal hormones. With gonadal activity, growth is slowed and eventually union takes place between the epiphyses and diaphyses of the bones. If gonadal hormone is present early and in sufficient amount, epiphyseal union is hastened and dwarfism results. A slender build, with disproportionately long arms and legs, occurs with diminished gonadal secretions. In all cases of hypo² and hyperpituitarism it is advisable to take stereoradiographs of the skull, paying particular attention to the pituitary fossa in order to eliminate the rare cases of tumour formation causing endocrine abnormalities.

Sufficient has been said to show that a great deal can be deduced concerning the endocrine balance of the individual by noting the skeletal measurements, the epiphyseal development, and the genital structure and function. This is particularly the case in childhood and many examples will appear in the succeeding chapters. Routine measurements alone, if repeated over a period, are of the greatest value in detecting endocrine disorder in the early stages, and we think that much trouble at and after adolescence could be avoided if the measurements described above were used as a routine method of examination in our schools. Measurement of the height and weight alone are not sufficient, for no evidence is obtained of the balance between long-bone and short-bone growth, which is the most important single conclusion which can be obtained from body measurements.

For convenience in assessing the development of young children, the following details are appended :

The normal birth weight is between 6·2 and 8·6 lb. : ossification centres are then present at the lower end of the femur, the head of the tibia, the astragalus, the calcaneus, and the cuboid bones of the foot : at two months the posterior fontanelle closes and at about this time the child should

commence to hold up its head : at three months the normal child should attempt to grasp at near objects and conjugate movements of the eyes should be well established : at five to six months it can roll from back to stomach, sit up and begin to recognise individuals : the lower central incisors should appear between six and eight months : at seven months it can grasp its feeding-bottle : at nine months it can pull itself up and also sit and balance on the chamber for defaecation ; and at about this time it begins to utter a few monosyllables such as " mum " and " dad " : the four upper incisors are erupted at the end of the first year and the lower lateral incisors and four anterior molars have appeared by another three months : at eighteen months the anterior fontanelle closes, the child can feed itself with a spoon and can walk alone ; sphincteric control should now be established during the day, though occasional nocturnal incontinence of urine continues till twenty-four months.

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CHAPTER 4

CLASSIFICATION OF PITUITARY DISORDERS

THE classification of pituitary disorders which has been adopted in this book is as follows :

- (1) Childhood pituitary obesity.
- (2) Hypopituitarism.

This term is applied to patients with defect of growth and sex hormones of the anterior pituitary gland.

- (3) Hyperpituitarism.

This term is applied to patients who show excessive activity of growth and sex hormones of the anterior lobe of the pituitary. Pubertas praecox is classified under pituitary disorders as an extreme degree of hyperpituitarism.

- (4) Thyro-pituitarism.

This term includes those patients who show the same pituitary disorder as in childhood pituitary obesity but with a thyroid defect dating from birth.

- (5) Other rarer syndromes that are probably pituitary in origin include Simmonds's disease, Cushing's syndrome, diabetes insipidus, progeria.

The great majority of children suffering from endocrine disorder fall into one of the first four groups, thyroid syndromes being relatively infrequent. Pituitary tumours have not been included except where questions of diagnosis arise.

Childhood Pituitary Obesity

Under this heading we have included those cases usually classed as Fröhlich's syndrome (without tumour), dystrophia

adiposo-genitalis, and under Engelbach's term adiposo-genital pituitarism. We have not adopted any of these terms because the first is better used only in a historical sense, and the others do not cover all the cases here described. We think that the evidence presented in the following pages shows that we are dealing with an endocrine syndrome rather than a collection of over-fed children. This hypothesis is strongly suggested by the family history, by the frequent spontaneous onset of obesity, by the general characteristics of the condition, causing the children to resemble one another, and by the signs suggesting hypothalamic involvement. There is sexual under-development in most of the boys and in some of the girls; in other girls the menarche appears at the normal time and in a considerable number it is very early. This suggests an involvement of the pituitary or the pituitary and hypothalamus, because growth, adiposity, and sexual development are pre-eminently functions of these areas. We have also pointed out, below, how the cases with considerable overgrowth merge into the hyperpituitary group, how the cases with growth defect merge into the hypopituitary group, and in the case of the girls there is a corresponding variation in sexual development. We are not supporting the view that this is primarily a hypofunction of the pituitary gland, but that there is evidence of pituitary imbalance; something more significant than gross over-feeding. The anomalies of development in children are mainly due to variation in the normal physiology; there are numberless variations which when slight, pass unnoticed, and when gross, receive the name of a syndrome. One of our chief interests has been tracing the connection from one syndrome to another. The cause of the obesity is obscure; it may be connected with the hypothalamus, but recent work suggests that pituitary-pancreatic interaction may be at fault.

We are aware that the use of the term pituitary in this class of case is open to criticism, but we think that it is justified on the clinical evidence, and if interest is aroused the present neglect of the fat child in this country may be remedied.

General Characteristics

The condition in the past has only been recognised at or after puberty when genital abnormality has become obvious, but it can be diagnosed in the juvenile and infantile years once the characteristics are grasped. There is a strong hereditary basis for the disorder, which will be clearly shown in the analysis of family histories, and the personal records of many patients show that obesity dated from birth or from a very early age before exogenous causes could operate. The first symptom is obesity which may develop gradually from birth, may arise spontaneously at any time during childhood, most often in the juvenile years, or may follow an acute infection. Obesity in childhood is a subject of the greatest importance. Although a loss of weight is always regarded with anxiety, a sudden gain of weight amounting to 50 per cent of the total weight of the child is often looked upon as evidence of good health. On the contrary, such a gain of weight is almost pathognomonic of endocrine disorder, and we emphatically contradict such statements as the following, which are to be found in standard textbooks: "The label of pituitary obesity is too often applied to fat children, the majority of whom owe their obesity to over-eating and insufficient exercise rather than to any definite endocrine abnormality". This opinion is responsible for much endocrine disorder being overlooked, for it is usually possible to distinguish obesity due to over-feeding from obesity due to endocrine cause. Besides the adiposity and genital hypoplasia or lack of function, the following symptoms may be found: excessive appetite or thirst, attacks of somnolence, enuresis, mental instability, and fits which may resemble major or minor epilepsy.

These children form a class with the following characteristics (see Plates No. 1 to 14). They have a pink-and-white or ruddy complexion, and two types of facies are found: the first with rounded cheeks, a very high colour, and neat features; the second with blunter features and a bloated plethoric appearance, the latter type being more common. The characteristic facies can also be picked out in adult

cases throughout life. The children with the plethoric facies look older than their age, and on improving with treatment they look younger again. Fat is mainly around the pelvis, in the breasts, on the mons veneris, and on the thighs. The pelvic fat often starts abruptly about the level of the umbilicus and extends down to the junction of the middle and lower third of the thigh. In adult patients a distinct cuffing may be present at that point.

Abdominal adiposity is often excessive, and the fat has a puckered appearance which is best described as "quilted", similar to that seen in women after the menopause and obviously abnormal in a small child. A pad is present over the mons veneris, and the thighs are so fat that no light can be seen between them when the child stands with heels together, a condition which is abnormal in the male sex in youth and adolescence, although not abnormal in the female. In older children the breasts are usually very large, and in both sexes fat often runs in folds from this area into the axilla. The shoulder girdle is more normal than the pelvis and the arms and the legs below the knee may be free from excessive fat, as are the hands and feet, but usually there is some excess in these areas. In the younger children obesity is more general, becoming localised as they grow older. The ligaments of all the joints are very lax, and with excessive weight this leads to kyphosis, flat-foot, and genu valgum, the last deformity being accentuated by the fat on the thighs, and the three together giving a typical stance well illustrated in Plates No. 1 and 2. Excess of growth hormone causes a height above normal and good development of the skull, facial bones, and teeth. The last may be above normal size, especially the upper central incisors, and owing to the growth of the jaws the teeth may be widely separated; but the condition of the teeth is excellent, decay being very rare. The fingers are tapering, and the skin is smooth and fine and rather hairless. In boys the genital organs show various degrees of under-development which can be recognised at an early age, and in some cases the testes are imperfectly descended. In both sexes at puberty the development of secondary sexual characters may be delayed or absent, or

takes place imperfectly. Menstruation may start unusually early, or it may be normal or delayed. If it begins at the proper time, it may remain irregular and painful for several years. The intelligence of these patients is at or above the normal level, but the usual emotional development at puberty may be delayed in those patients who show sexual hypoplasia.

Three illustrative case histories will be given. The first is the most usual type of case.

CASE NO. 10.—Plates No. 1 to 5. A boy aged $10\frac{1}{2}$ years.

Family History.—There are no other children and the parents are healthy.

Past History.—The patient developed normally and without any important illness, except chorea when he was 5 years old. Five years later he attended hospital for squint but was found to be too nervous to undergo treatment in the orthoptic department and was transferred to the medical side. There the history was obtained that during the last eighteen months he had gained a great deal of weight.

On examination, he was a very nervous boy of normal intelligence. Adiposity was the most prominent feature. This was conspicuous around the pelvic girdle and on the thighs, between which no light could be seen when the legs were together. The face was fat and had the characteristic bloated look. The plates show the typical stance with slight kyphosis and genu valgum due in part to adiposity and in part to hypotonic ligaments. Comparison with the normal figures showed the excess in weight and in chest and abdominal measurements which are found in these patients, the height falling within normal limits. The genital organs were under-developed; the right testis could be felt in the inguinal region; the left was absent.

A radiograph of the skull showed no abnormality and the development of the epiphyses corresponded to his age. The sigma reaction of the blood-serum was negative.

Further History.—The general progress can be followed most easily by comparing the plates and the table of measurements with the following account. The patient was given a 6-line diet and whole pituitary powder nasally (see p. 93) for twelve months. The striking change in his physical appearance (Plate No. 3) was accompanied by an equally important improvement in his mental condition and he became able to co-operate in orthoptic treatment. During the year the penis enlarged and the right

testis descended, he grew $1\frac{1}{2}$ in., and a loss of no less than 26 lb. in weight caused a reduction of 5 in. in both chest and abdominal measurements.

The diet was increased to 7 lines during the second year of treatment with extra protein as required; the pituitary powder was stopped and Pregnyl substituted in 500 rat unit doses once weekly for four months to accelerate genital development. The next measurements, which were taken when he was 12 years and 4 months old, showed that he had grown $1\frac{1}{4}$ in. but the extra food taken had led to a gain of 23 lb. The testes had grown to normal size but the penis was still small. He was stated to be better than he had been for years. During the third year he continued to put on weight, so he was ordered to adhere strictly to a 7-line diet; but no other treatment was given and the measurements at the end of the year, when he was 13 years and 4 months old, showed a gain of 16 lb. But despite this gain comparison of the chest, abdominal, and height measurements showed that improvement had been maintained. As there was a further rise of weight in the fourth year, and as the penis was still somewhat underdeveloped, injections of whole pituitary gland (gr. xxx) were given twice weekly for six months. By the age of $14\frac{1}{2}$ years he had grown a further $4\frac{1}{2}$ in. which largely offsets a gain of 15 lb. It is interesting to note that the chest measurement was now 1 in. more and the abdominal measurement 2 in. less than they were four years before. The plate shows a great general improvement but a feminine type of figure, with a pelvic band of fat, and genu valgum are still present, although the genital organs are normal. He was then instructed to take an ordinary diet and was seen again when he was 16 years old. The table and plate show his growth and development, but an increased diet had led to abnormal increase in weight. The voice was breaking, there was a good deal of acne on the skin, there was no appearance of genu valgum, and in his clothes he looked normal. He was advised to restrict his diet.

This patient was chosen for detailed description for several reasons: he was under observation for some time, he derived great benefit from treatment in the initial stages, and he showed the response of the genital organs to stimulation. But he also showed what is equally important, that residual signs of pituitary disorder were left when treatment had been concluded. These signs are not always so prominent as in this patient, as Plates No. 8 and 11 show, but some evidence can usually be found. Few patients become able to tolerate an

ordinary diet, the majority requiring dietary restrictions indefinitely.

Measurements—

Case No. 10	Age					
	10½ Years	11½ Years	12½ Years	13½ Years	14½ Years	16 Years
Head .	20.5 in.	20.5 in.	20.5 in.	21.0 in.	21.0 in.	21.5 in.
Chest .	30.0 "	25.0 "	27.0 "	26.0 "	31.0 "	36.0 "
Abdomen	32.0 "	27.0 "	28.0 "	29.0 "	30.0 "	34.0 "
Span .	57.0 "	57.0 "	59.0 "	62.5 "	66.0 "	69.0 "
Height .	55.0 "	56.5 "	57.75 "	60.5 "	65.0 "	67.5 "
Lower M.	28.75 "	30.0 "	30.75 "	32.25 "	35.5 "	36.0 "
Upper M.	26.25 "	26.5 "	27.0 "	28.25 "	29.5 "	31.5 "
Weight .	96.5 lb.	70.0 lb.	93.0 lb.	109.0 lb.	124.0 lb.	156.0 lb.

CASE No. 28.—A girl aged 16 years and 8 months. This case is one in which adiposity starting at the age of 11 did not pass off at puberty and in fact became steadily worse until treatment was instituted.

Family History.—The mother is of a nervous type and the father is very tall, as are all his family. There are no other children.

Past History.—The patient developed normally until the age of 11, when she had a prolonged illness diagnosed as pyelonephritis. After this there was a continuous rise of weight. Menstruation started at 14 years but never became regular, and there were long periods of amenorrhoea.

On examination, she was an intelligent girl but lately had become "slow off the mark" and lacking in power of concentration. She showed the usual pink-and-white complexion and obesity of hips and breasts. The thighs were fat, but the arms and legs below the knees were normal.

The measurements were as follows :

Case No. 28				Patient	Normal
Head	.	.	.	21.5 in.	21.75 in.
Chest	.	.	.	36.5 "	30.3 "
Abdomen	.	.	.	32.0 "	25.2 "
Span	.	.	.	67.0 "	62.0-66.0 in.
Height	.	.	.	64.0 "	61.4-65.6 "
Lower Measurement	.	.	.	34.5 "	30.0-33.0 "
Upper Measurement	.	.	.	29.5 "	30.0-33.0 "
Weight	.	.	.	162.0 lb.	102.0-126.0 lb.

These measurements show the same characteristics as in the previous case. No further investigations were undertaken.

Subsequent History.—The patient was given a Lawrence's line diet and chorionic gonadotropin (Antuitrin S. 1 c.cm.) every other day for nine months, then 1 c.cm. weekly for five months. At the end of that time she looked and felt very much better, her school work had so improved that she had gone to the top of her class, menstruation had been regular for several months, and she had grown $\frac{1}{2}$ in. and lost 7 lb. in weight. Her age was then nearly 18, and treatment was restricted to a small dose of thyroid for a few months. She continued to lose weight on a normal diet and periods remained regular although painful. At the age of 20 years and 4 months she looked perfectly well; the weight was 129 lb.; the chest measured 34.5 in. and the abdomen 28 in. Shortly after this the patient married and became pregnant immediately. Careful observation was made during the pregnancy, but there was no abnormal gain of weight and a healthy child was born without difficulty at full term.

The interest in this case lies in the fact that the patient's health had been extremely unsatisfactory from the age of 11 years until the age of 16 years. Search for various causes had been made but endocrine disorder was not suspected. Immediate improvement occurred when treatment was started and we attribute a great deal of the improvement to the effect of a restricted diet.

CASE NO. 94.—Girl aged 10 years and 3 months. There is no family history of endocrine disease and the patient is an only child. She was very thin until 8 years old when she had an attack of scarlet fever. Following this she gained weight rapidly, for which symptom she was brought to hospital.

On examination, she showed adiposity of the pelvic girdle and the upper two-thirds of the thigh without excessive fat on the rest of the body, the weight being 25 lb. above the maximum normal for the age and 15 lb. above the maximum normal for the height. Radiographic examination of the skull was normal and the epiphyses showed slightly advanced development. The B.M.R. was -12 and the sigma reaction of the serum was negative.

Subsequent History.—She was given a 7-line diet and at once became more energetic, while the appetite, which had been excessive, gradually became normal. The progress can be seen from the measurements. In five months she grew 1 in. and lost 12 lb., which brought her weight to within $\frac{1}{2}$ lb. of the normal range for the height. The appearance was much improved,

although a considerable pelvic girdle remained. By the time she was 11 years and 9 months this had disappeared and she looked normal, the weight being within the normal range for the height. Although the chest and abdominal measurements remained steady, the weight rose sharply with the approach of puberty, but the weight at 13 years and 3 months was only 7 lb. in excess of the maximum for that age and only just above the optimal weight for the height. The first menstrual period occurred on the 14th birthday. The height measurements show an endocrine imbalance. At 10 years of age the lower measurement exceeds the upper by 2.5 in. instead of being almost equal, and this disparity had increased to 6.75 in. by the age of 13 years, giving a very badly proportioned skeleton.

Case No. 94	Age				
	10 $\frac{1}{2}$ Years	10 $\frac{3}{4}$ Years	11 $\frac{3}{4}$ Years	11 $\frac{9}{10}$ Years	13 $\frac{3}{4}$ Years
Head .	20.0 in.	20.0 in.	20.0 in.	20.0 in.	20.0 in.
Chest .	29.0 "	27.5 "	26.0 "	27.0 "	28.5 "
Abdomen	30.0 "	29.0 "	29.0 "	28.0 "	29.0 "
Span .	56.0 "	56.0 "	58.0 "	60.0 "	63.0 "
Height .	55.5 "	56.5 "	57.25 "	59.25 "	62.25 "
Lower M.	29.0 "	30.0 "	30.75 "	32.25 "	34.5 "
Upper M.	26.5 "	26.5 "	26.5 "	27.0 "	27.75 "
Weight .	96.0 lb.	84.0 lb.	86.0 lb.	95.0 lb.	108.0 lb.

This case is reported because it is representative of a large and important group. The sudden development of obesity indicates an endocrine upset, in this patient due to infection, but often occurring spontaneously. This is the type of patient often dismissed as "juvenile obesity"; even when only one member of a family is affected, the degree of obesity is far outside the normal limits, and is of a type usually associated with pituitary-hypothalamic disturbance.

As there was no history of endocrine disorder in the family the constitutional factor was probably not pronounced and this child might have become normal in a few years without treatment, when the endocrine upset due to the infection had passed off. But we have no means of foreseeing this, and the history of many of our patients who first attend when they are older shows that this happy result does not always occur; sexual function was not depressed and developed without endocrine treatment. The point we wish to emphasise is

the importance of treating these patients, because immediate improvement can be obtained. Within five months this child had been greatly benefited by the simplest of methods. Improvement was entirely effected by dieting. She was given a very small dose of whole gland thyroid ; but this was given as a placebo, because it is difficult to ensure steady attendance at hospital unless some treatment besides dieting is prescribed. (We often give a placebo tablet consisting of half a grain of sugar for this purpose.) The diet has been increased but is still being adhered to and will probably need restricting until adult life is reached. A similar case is illustrated in Plates No. 9 to 11.

AN ANALYSIS OF 125 CASES OF PITUITARY OBESITY IN CHILDHOOD

Endogenous Aetiology

An analysis of the family history will give some facts of interest, which are set out in the following tables :

FACTS OF ENDOCRINE INTEREST IN THE FAMILY HISTORY OF 72 GIRLS

- 6 mothers showed thyroid disorder—
 - 2 showed enlargement.
 - 2 hyperthyroidism.
 - 2 died in acute thyroid crisis (one under our own observation).
- 15 mothers were or had been very stout—
 - 1 was stout as a child and is now normal.
 - 2 were stout as children and are still stout.
 - 1 was stout as a child and increased the weight by one stone after each of four successive pregnancies.
 - 1 increased weight to 18 stone after birth of patient.
 - 1 became stout after the birth of a 14 lb. child.
 - 1 had three children after the patient, each of 10 lb.
 - 1 increased several stone after pregnancy at 40 years.
 - 7 were stout (no further information).
- 1 mother had diabetes mellitus.
- 11 fathers were or had been stout—
 - 1 was very fat at 18 years, subsequently became normal.
 - 1 was very fat as a boy and remains stout.
 - 9 were stout (no further information).
- 1 father had diabetes mellitus.

2 brothers had pituitary obesity.

1 sister had hypopituitarism (growth defect).

6 near relatives had diabetes mellitus, consisting of—

5 grandmothers (one of these had goitre).

1 aunt.

16 near relatives were stout, consisting of—

6 grandparents. Of these one weighed 20 stone, another 22 stone after pregnancy, and one who had been fat when 16 years old showed no menstrual periods until 22 years old and then had three very big children.

4 aunts. Two resembled the patients in type, one had been fat as a child and had a fat daughter.

4 uncles (one weighed 18 stone).

1 aunt had a thyroid adenoma (her son is noted on the next line).

1 cousin had pituitary obesity.

There was a history of obesity in the maternal relatives of one family, and in the paternal relatives of another, but exact particulars were not known.

No relative is included more than once in the above table.

These facts were taken from the history of 44 patients out of a total of 72 ; in the other patients nothing was noted.

FACTS OF ENDOCRINE INTEREST IN THE FAMILY HISTORY OF 53 BOYS

4 mothers showed thyroid disorder—

2 showed enlargement.

1 showed hyperthyroidism.

1 gave a history of puberty goitre.

9 mothers had a history of obesity—

2 were fat as children and had become normal.

3 became fat after childbirth.

1 was stout and below normal height.

3 were stout (no further information).

2 fathers were stout—

1 father showed evidence of hypogonadism.

1 father stout (no further information).

2 sisters showed pituitary obesity.

1 brother had been fat and was now thin.

4 near relatives had diabetes mellitus, consisting of —

3 grandmothers.

1 great-grandmother.

3 aunts had thyroid disease, two had goitre, one exophthalmic goitre.
9 near relatives were very stout, consisting of—

2 grandfathers.

5 aunts.

2 uncles.

Diabetes was present in one patient's family, obesity in another, and late sexual development in a third, without exact particulars being noted.

No relative is included more than once in the above table.

These facts were obtained from the histories of 24 cases out of the 53 ; in the other cases nothing was noted.

These family histories furnish undeniable evidence of endocrinopathy but they are very far from complete, for they include all our earlier cases, in which not nearly so much care was taken in obtaining particulars. Since we began to question every patient about abnormality of weight and stature and the presence of diabetes and goitre in relatives, much additional information has been forthcoming. It is interesting to note that there is as much or more evidence of endocrine disorder in the histories of the girls as of the boys, and it is a striking fact that the brothers and sisters of patients were usually normal, which would scarcely be the case if pituitary obesity were due to gross over-feeding of a normal child. It will be seen that in many cases the obesity is probably inherited. At first sight this seems to indicate that in such cases endocrine influence does not play any part, but this requires further consideration. For example, in one family the mother is obese, one daughter is fat owing to pituitary obesity, and another daughter shows growth defect. Most of the cases of obesity regarded as due to inheritance may just as truly be regarded as due to endocrine factors. This is not to deny the influence of genetic inheritance on bodily constitution, but to point out that there is in fact an inheritance of endocrine constitution.

Obesity in the mother is such an important point that it deserves further comment. Engelbach (2) points out that a woman who permanently gains an abnormal amount of weight during pregnancy is probably suffering from endocrine disorder and that any rapid rise of weight during pregnancy calls for examination. The successive development of

chloasma, osteophytic overgrowth of the bones, or a tendency towards acromegalic facies would be additional evidence that the pituitary gland was not undergoing the normal physiological reaction. The B.M.R. should be determined in these patients to find out if there is a normal thyroid stimulation to metabolism, and treatment with pituitary or thyroid gland may be very beneficial in restoring glandular function and preventing an abnormal gain in weight. Fat patients are liable to have big babies and Englebach states that they too suffer from hypothyroidism. This is true in some instances, but from our own experience we cannot say how frequently this occurs.

Exogenous Aetiology

Examination of our series shows that exogenous factors are not nearly so important as endogenous. Birth injury may be a cause and give rise to what is called the cerebral type of this disorder through damage to the hypothalamic-hypophyseal mechanism, and doubtless the same mechanism is present in those cases which are due to tumour, basal meningitis (syphilitic or otherwise), encephalitis, or fractures of the base of the skull. None of these conditions except birth injury figures in our list. In this case there was a difficult breech delivery with severe injury to the child, who later showed mental deficiency, and this case really falls into a separate class. The most important precipitating factor is acute infection, which immediately preceded the development of obesity in 20 of the 125 cases: appendicitis, pleurisy, rheumatic fever, chicken-pox, diphtheria, influenza, chorea, croup, erysipelas, pyelonephritis, and nephritis accounting for 11 cases; whooping-cough, scarlet fever, and pneumonia accounted for two cases each, and measles for three cases. Seven cases followed the operation for tonsils and adenoids. Considering the prevalence of infectious diseases in children the importance of this history is doubtful, and these figures illustrate the relative importance of the constitutional factor.

Analysis of Symptomatology and Physical Characteristics

Our 125 cases consist of 53 boys and 72 girls, aged 3 to 17½ years when first seen. The upper limit was arbitrarily chosen for the purpose of this book because we have patients

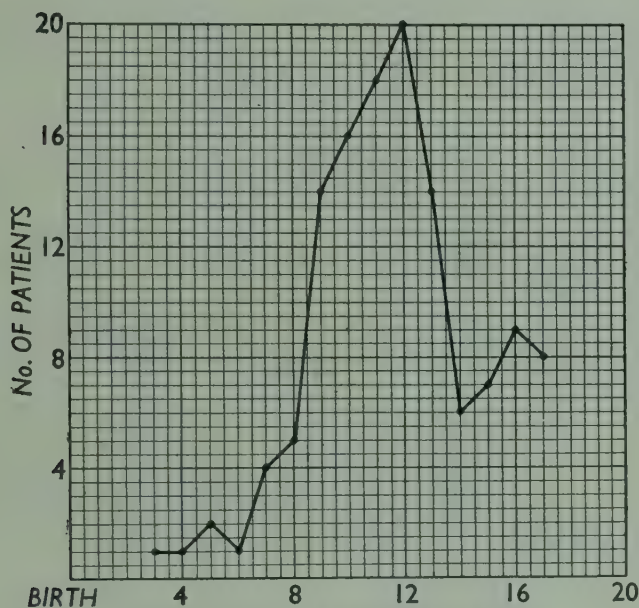


FIG. 1.—Age of patients in years.

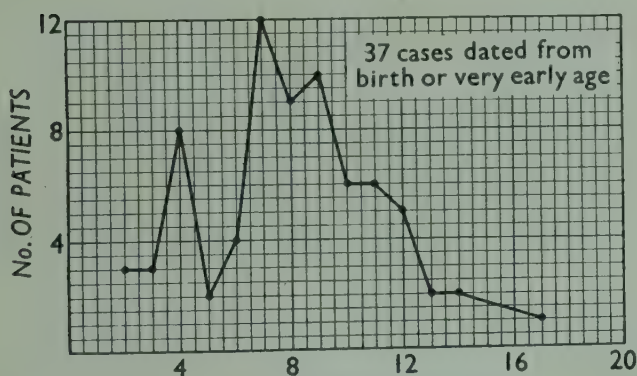


FIG. 2.—Age of patients in years.

throughout adult life under observation. Fig. 1 shows the ages of the children on first attendance at hospital for pituitary obesity, and Fig. 2 shows the age of onset of obesity in 110 cases in which a history could be obtained : 37 of them were

noted as having always been plump, and though some were brought up for a recent increase of weight, they were all counted as dating from birth. Some points of interest arise from these figures. It is obvious that infantile obesity is completely neglected, that most cases of pituitary obesity arise in the infantile and juvenile years, before the age of puberty, and that there is a delay of several years before treatment is sought. The importance of noticing obesity in the early years is emphasised, for it is often the earliest indication of endocrine disorder; but the analysis of our records brings out other interesting symptoms and signs.

Symptoms.—The fact that these children may have a small appetite is sometimes given as one of the distinctions between pituitary obesity and obesity due to over-eating. In a few of our cases it was stated that the appetite was small, but in a greater number, 12, the appetite was extremely large; in 9 of these cases the consumption of fluid was also excessive, and in 8 further cases, although the appetite was normal, the consumption of fluid approached that found in diabetes insipidus. Some cases developed hunger or thirst suddenly, and we consider that this is probably a symptom of a crisis in pituitary function. The toxic crisis of thyroid disease is well known, but such a possibility in relation to other ductless glands is not so generally recognised. We are convinced, however, that it occurs, and it will be referred to again (see p. 273).

Bilious attacks and enuresis were each noted four times in our series, probably no more than would be expected in any series of children attending hospital. Occasional glycosuria with a normal blood-sugar was found in one case.

An important symptom was the occurrence of fits. The following instance is a case in point. The patient (Case No. 37), a boy of 11 years, was brought up to hospital with the history that he had gained weight steadily from birth. He was 51 lb. above the maximum weight for his age and the genital organs were under-developed. All his life he had been subject to fits which consisted of twitching of the face followed by unconsciousness during which he passed urine,

and to minor attacks resembling petit mal. There was no evidence of any intracranial lesion. He was dieted and treated with chorionic gonadotropin and pituitary powder for fifteen months. Fits ceased as soon as treatment began and did not recur during the four years he was under observation. Another patient (Case No. 19) was a girl, aged 11, who had several nocturnal attacks a week, consisting of muscular flaccidity and sweating, followed by pain in the shoulders; these attacks also ceased following treatment. Two patients gave a history of attacks of unconsciousness, one at the age of 2, the other between the ages of 3 and 7. These passed off spontaneously. Another girl (Case No. 92) had a history of attacks between the ages of 2 and 7, which consisted of facial spasm followed by unconsciousness for a few minutes. These attacks recurred at the age of $15\frac{1}{2}$ years and ceased when treatment was instituted at $16\frac{1}{2}$ years. We attach considerable importance to this matter, because we have noticed fits in other pituitary conditions in children, and we think it should be borne in mind before the diagnosis of idiopathic epilepsy is made.

In 97 patients a note was made of the mental condition and development, and in every case there was a normal history regarding the time of onset of talking and walking. In 54 cases the intelligence was normal as judged by examination and by the record at school; 28 children were above average intelligence, many of them being of scholarship standard. Of two patients who showed mental deficiency one has already been mentioned as having had birth injury and in the other no cause for the deficiency could be found. Thirteen other patients were somewhat backward for their age, and of these nine had treatment, with considerable improvement in six of them. Some of the patients were referred to us in the first place for mental abnormality, but further discussion of this will be left to a special chapter (see Chapter 14). We noted in several instances that the children had lost interest in their school work and become dull and lazy coincidentally with a large increase of weight. These children rapidly improved when treated, dieting alone being sometimes sufficient. Mental development in

this syndrome is therefore not delayed, and the children are probably slightly above normal in intelligence.

Physical characteristics.—In all patients routine measurements were taken and repeated during treatment, and these afforded help in diagnosis and a guide to the effect of treatment. The height was taken in 124 cases; 66 fell within normal limits, 42 were above the maximum, and only 16 were below the minimum for the age. The patients above the normal showed excess measurements varying from 0.5 in. to 7 in., the average being 2 in.; the patients below the minimum varied from 0.5 in. to 7 in. below the normal minimum, the average being 1.4 in. Of those patients who fell within normal limits no less than 39 were above the mean normal, while 27 were at or below it; so we can see that the mean height in this syndrome is much above the normal average. The measurement of the span corresponded to the height, and the figures need not be quoted. Examination of the relation between the upper and lower measurements showed what one would expect; the average length of the lower measurement was above normal, for it attained the same length as the upper measurement at an earlier age than usual and thereafter exceeded its normal relation to the upper measurement. The fact that growth is generally above normal in these cases and not restricted to the long bones is shown by the cranial measurements. In 125 patients, 43 showed normal measurements, 65 showed measurements above the mean normal, and 17 were below the mean normal. The weight, chest, and abdominal measurements showed the most striking departures from normal. In 117 patients, 113 showed weights varying from 1 lb. to 149 lb. in excess of the normal maximum. The following table shows clearly the variation of weight above normal in the series; it is especially striking when we remember that many of these children were very young:

Lb. in excess of normal maximum	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71 and over
No. of cases	7	24	33	15	14	8	8	4



PLATE 1. CASE 10.

Age 10½ yr.; Wt. 96 lb.; Ht. 55 in.
Testes undescended, appearance of
scrotum misleading.



PLATE 2. CASE 10.

Age 10½ yr. Obesity pronounced: typical stance.



PLATE 3. CASE 10.

Age 11 yr. 3 mth.; Wt. 70 lb.; Ht. 56½ in. Great loss of weight in 9 months.



PLATE 4. CASE 10.

Age 14½ yr.; Wt. 112 lb.; Ht. 65 in. Feminine contours, cf. with hypergonadism.



PLATE 5. CASE 10.

Age 16 yr.; Wt. 156 lb.; Ht. 67 in. Pelvic obesity, feminine distribution of pubic hair.



PLATE 13. CASE 123.

Age 10 yr.; Wt. 112 lb.; Ht. 53 in. Excessive trunk obesity, slender arms and legs.



PLATE 6. CASE 15.
Age 13 yr.; Wt. 245 lb.;
Ht. 68 in.; Abd. 46 in.



PLATE 7. CASE 15.
Age 13 yr. 10 mth.; Wt. 206
lb.; Ht. 70 in.; Abd. 41 in.
In 10 mth. patient not recogni-
sable as same boy.



PLATE 8. CASE 15.
Age 15 yr. 7 mth.; Wt. 200 lb.;
Ht. 71½ in.; Abd. 38 in.
Genu valgum gone. Genitals en-
larged.



PLATE 9. CASE 141.
Age 11½ yr.; Wt. 147 lb.;
Ht. 61 in.



PLATE 10. CASE 141.
Age 11½ yr. Cf. with Plate 2.



PLATE 11. CASE 141.
Age 12½ yr.; Wt. 126 lb.; Ht.
63 in. Result of one year's
dieting only.



PLATE 12. CASE 122.

Age 10 yr.; Wt. 117 lb.; Ht. 55 in.;
Abd. 33 in. Note quilted fat. Cf.
with Plate 13.



PLATE 14. CASE 105.

Age $14\frac{1}{2}$ yr.; Wt. 59 lb.; Ht. $47\frac{1}{2}$ in. Childhood
pituitary obesity and growth defect. Cf. with
sister on right aged $11\frac{1}{2}$ yr., Wt. 57 lb., Ht. 53 in.



PLATE 15. PATIENT A9.

Age 28 yr.; Wt. 238 lb. Obesity
started 14 yr. Periods began
11-12 yr. Always regular. Note
plethora and aged appearance.



PLATE 15A. PATIENT 10.

Age 33 yr. Always fat. Men-
struation started 14 yr.,
irregular until 16 yr., amenor-
rhoea since 32 yr. with further
gain of weight.

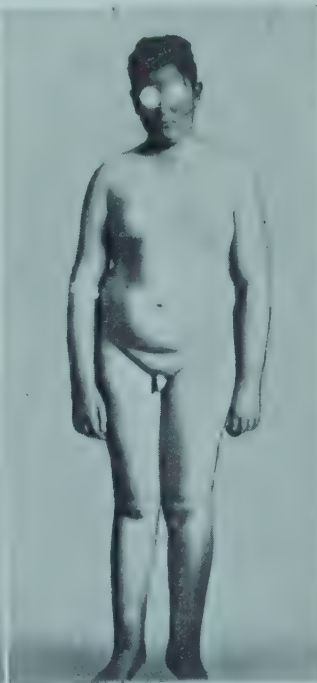


PLATE 16. CASE 118.

Age $15\frac{1}{2}$ yr.; Wt. 150 lb.; Ht.
 $62\frac{1}{2}$ in. Infantile sexual
development. No treatment.



PLATE 17. CASE 61, on right.

Age 16 yr.; Wt. 39 lb.; Ht. 41 in. Showing growth and sex defects and compared with normal child 6 yr. old.



PLATE 18. CASE 61.

Age 18 yr.; Wt. 64 lb.; Ht. 45 in. Shows considerable effect of treatment.



PLATE 19. CASE 74, on left

Age 11 yr.; Wt. 154 lb.; Ht. 65 in. Breasts developed, pubic hair present. Cf. with

PLATE 20. CASE A5, on right.

Age 20 yr.; Wt. 75 lb.; Ht. 55½ in. With growth and sex defects.



PLATE 21. CASE 63.

Age, 17 yr.; Wt. 84 lb.; Ht. 57½ in.

Growth defect and diabetes insipidus.

Genital organs nearly normal.

Only 4 patients were below the minimal weight for their age—2 lb., 2 lb., 5 lb., and 29 lb. respectively ; the last was at the minimal height and showed a slight adiposity of the trunk, the chest and abdominal measurements being in excess of the mean normal. In every patient, except two in whom the measurement was normal and one in whom it was omitted, the chest measurement was in excess of the mean normal, varying from 1 in. to 15 in. The average excess in 122 patients was 5.8 in. The abdominal measurements were phenomenal ; one boy of 13 had an abdominal measurement 21.5 in. in excess of the mean normal (see Case No. 15, Plate No. 6). This was the greatest, the smallest being 1 in. and the average excess in 124 cases was 8.4 in. We must consider the epiphyseal development in relation to these measurements. The epiphyses were radiographed in 87 instances. In 45 the development was normal, in 29 it was advanced, and in only 13 instances was it slightly retarded. There was only a slight advance in development, 2-3 years in most cases, but this finding proves that hypothyroidism plays little part in the syndrome, since thyroid deficiency causes delay in the appearance of the centres of ossification. The advanced development is associated with the increased growth of the bones. Radiographic examination of the pituitary fossa was made in 78 cases, in two cases it was partly or wholly bridged over, and in two cases it was small, and in one case large ; the rest were normal.

The consideration of the somatic and genital development brings out other interesting points. We find that there is a general bodily over-growth which is not solely due to a disproportionate growth of the long bones but is present in the flat bones also. This suggests a dissociation in this syndrome between the pituitary growth and sex hormones, the former being normal or present in excess in most cases, while the latter are deficient in many cases. The activity of the growth hormone varies considerably, some patients being very big indeed ; for example, Case No. 15 (Plate No. 6) was a boy aged 13 years whose height was 68 in., and so far as growth hormone is concerned the case is one of hyperpituitarism, but it differs from that condition in showing genital

under-development and in the presence of characteristic obesity. On the other hand, we find patients who are below the normal height. They are fewer but nevertheless afford a link with those cases of pituitary dysfunction characterised by extreme under-growth and classified as anterior hypopituitarism. The best example in our series is Case No. 6, a girl who was 7 in. below the minimum height for her age of 16 years. We have classified another patient (No. 105, Plate No. 14) under the heading of anterior hypopituitarism because her main characteristic is under-growth—she is 11 in. below the minimum for her age of 14 years—but she could equally well have been included in this group, because she shows the characteristic obesity and also sexual dystrophy. The patients in the hypopituitary group are usually thin and puny, and the above patient is an exception in showing pituitary obesity, so clearly she forms a link between the two conditions. She is an example of what has been described in the past as the classical Fröhlich type, showing retardation of growth, obesity, and sexual under-development. Thus different combinations of growth and sex development give rise to a great variety of clinical pictures, so that cases could be placed in a continuous series to show their relationship to one another and to hypopituitarism (growth defect) at one end of the scale, and to hyperpituitarism at the other (see Plates No. 1 to 14).

Genital under-development is a striking feature in the male cases; in our series of 53 there was normal development in 4, general under-development in 38, and in 11 under-development associated with imperfect descent of one or both of the testes. Relatively few cases showed imperfect descent of the testes, and this is possibly another consequence of the fact that thyroid defect is not an important factor, so that initial differentiation, which is largely under thyroid control, takes place, and development proceeds normally, until a halt occurs owing to pituitary deficiency. Eight male patients first attended when aged 14 to 17 years, and in all of these the sexual changes of puberty were much retarded. In view of the statement that all obese boys develop at the normal age, we give particulars of these eight cases :

Case No.	Age in Years	Genital Development
222	14	Small.
181	17	Small. Left testis $\frac{1}{2}$ size. Right testis imperfectly descended. Pubic hair scanty. Does not shave.
29	$14\frac{1}{2}$	Small. No axillary hair.
27	$14\frac{2}{3}$	Very small. Very slight pubic hair. No axillary hair.
121	$15\frac{4}{5}$	Slightly small. No axillary hair.
118	$15\frac{1}{2}$	Very small. No axillary hair. No pubic hair.
90	$15\frac{3}{5}$	Infantile genitals, testes minute and imperfectly descended.
229	$15\frac{8}{12}$	Very small.

Genital under-development is not so prominent a feature in the female cases as in the male, but it is incorrect to state that all obese girls mature early or at a normal time. We have 19 patients who first attended between the ages of 14 and $17\frac{1}{2}$ years and particulars are given in the following table :

Case No.	Age in Years	Age when Menstruation started	Character of Menstruation and Sexual Development
4	$14\frac{1}{2}$	14	Regular.
71	$14\frac{3}{4}$	$13\frac{3}{4}$	Normal.
83	16	14	"
163	$16\frac{1}{2}$	12-13	"
124	17	12	"
89	$15\frac{1}{2}$	11	"
180	$17\frac{1}{4}$	11	"
96	$16\frac{1}{4}$	11	"
193	$15\frac{1}{2}$	11	Profuse.
26	$17\frac{1}{2}$	16	Regular.
21	17	17	Scanty pubic hair, no axillary hair.
28	$16\frac{3}{4}$	$13\frac{3}{4}$	Very irregular.
30	$15\frac{1}{4}$..	" "
111	16	14	Irregular.
92	$16\frac{1}{2}$	11	Still irregular, male distribution of pubic hair.
6	16	..	No periods, no pubic hair.
195	17	$14\frac{1}{2}$	Irregular.
224	$16\frac{1}{2}$	15	Irregular, about three times a year, genitals infantile.
205	16	15	Scanty and irregular.

The first five patients in the table are normal in every respect, the next three are normal except that they started menstruation at 11 years which we regard as early, the following eleven patients show some further abnormality. In general we agree that most of these patients menstruate and develop either normally or at what we regard as a precocious age, 10 or 11 years.

It is worth while considering what is the normal time for puberty to occur in boys and girls. To take the girls first, many authorities quote as wide a range as $10\frac{1}{2}$ years to 17 years for the menarche to occur (6). From the practical point of view it is necessary to take a narrower view or many endocrine imbalances will be missed, and it is not disputed that wide differences in stature are seen when comparing girls who mature early with those who mature at the age of 17 years. We regard the 13th birthday as the optimal time for menstruation to begin. If it starts before $11\frac{1}{2}$ years or has not started by $14\frac{1}{2}$ years, there is at least evidence of a variation so far from the optimal as to need observation. The figure for puberty in boys could be put between 13 and 15 years. We should observe closely those boys who showed puberty signs before the age of $12\frac{1}{2}$ years or no signs at all at the age of $14\frac{1}{2}$ years. Maturation in both sexes is a gradual process but late development in our experience is present to a significant extent in the histories of adult endocrine patients.

Further investigations.—A Wassermann or flocculation test of the child or the mother was carried out in 51 cases with a negative result in each case. Volhard's water-balance test was done on some of the children who suffered from excessive thirst, but no evidence of water retention was found. The determination of the basal metabolic rate offers some difficulties in children, but reliable results were obtained in 45 cases. The normal B.M.R. was calculated from the surface area derived from the height and weight, using the standards of Aub and Du Bois (7). If the more modern standards given by Webster (8) are used, the results in the table below require slight modification. The B.M.R. of the boys between $11\frac{1}{2}$ and 14 years should be increased by 2 per

FEMALE CASES : 29

Case No.	Age in Years	B.M.R.	Blood Cholesterol	Epiphyseal Development	Intelligence
4	14½	+10	..	Advanced	..
180	17	+2	..	„	N.
175	9½	+1	..	„	..
77	11	-1	192	N.	Rather below N.
239	13	-1	176	Advanced	N.
41	8½	-2	173	N.	N.
245	10	-3	273	Advanced	N.
71	15	-4	..	N.	..
110	12½	-6	..	N.	N.
234	13	-6	186	N.	N.
85	5	-7	..	N.	N.
78	5	-7	165	N.	..
193	15½	-7	149	Advanced	Above N.
212	13½	-7	175	„	N.
173	14	-9	154	„	Above N.
158	11	-10	..	N.	..
96	16½	-10
124	17	-11	163	N.	N.
76	8	-12	190	Retarded	N.
94	10	-12	156	Advanced	N.
113	11½	-12	208	N.	Above N.
114	9	-13	190	Advanced	N.
171	12½	-16	198	N.	Above N.
187	12	-18	..	Retarded	„
86	8	-20	223	..	Much above N.
163	16½	-22	..	Advanced	N.
141	11½	-22	262	„	Slow lately
101	3	-24	..	N.	Much above N.
182	10½	-25	151	N.	Rather slow

MALE CASES : 16

188	13½	+10	..	Retarded	Scholarship std.
91	13	+3	227	N.	Above N.
160	10	+1	..	Advanced	N.
209	13	±1	332	N.	N.
121	16	-3	170	N.	Above N.
126	11½	-5	230	N.	N.
194	10	-5	..	N.	..
179	13½	-6	..	Retarded	Above average
153	12½	-8	168	Advanced	N.
117	10	-10	165	N.	Below N.
185	11	-17	218	Retarded	..
207	9½	-17	112	Advanced	N.
33	13	-20	..	„	N.
11	9	-21	..	N.	Above N.
184	12	-21	181	N.	..
166	12½	-36	216	N.	N.

N. represents Normal.

cent and that of the girls between 11 and 13 years should be decreased by 2 per cent. In the table on p. 83 the results are given together with the blood cholesterol, epiphyseal development, and mental development of the patient where these have been noted. The low B.M.R. and the high cholesterol, where that was present, were not associated with evidence of hypothyroidism. Fasting blood-sugar estimations were normal in a number of cases.

Diagnosis

It should be emphasised here that childhood pituitary obesity is probably due to functional upset of the anterior pituitary gland or the pituitary-hypothalamic mechanism and is only in rare instances caused by a tumour. In the differential diagnosis of this condition it is necessary to distinguish between obesity without an endocrine basis and obesity which is the result of a hormonal imbalance. In the non-endocrine group the only condition likely to cause difficulty is obesity due to over-eating, which is emphasised in many textbooks as the usual cause of obesity in children. We have stated above that we entirely disagree with this view, for we have looked for these over-fed children in vain; they scarcely exist in the hospital class, and the well-to-do child usually works and plays too hard to develop obesity without organic cause. One of our colleagues looks after a preparatory school for seventy boys, and during the last five years all cases of obesity in that school have fallen into the pituitary group. The family history, the circumstances of the development of obesity, and the associated symptoms, signs, and measurements of the child give evidence of a syndrome which is as a rule easily distinguished from obesity due to over-eating. Sudden development of obesity in the juvenile years, without change of conditions, whether it occurs spontaneously or following an infection, is highly suggestive of this syndrome. The standard measurements of weight which have been used allow amply for normal variation and most of our cases far exceed these limits. Admittedly the diagnosis rests on the most sure grounds in those patients, male and female, in whom sexual under-development is

present after the age of puberty. But in small boys sexual under-development is usually quite plain, even after discounting the fact that the genital organs may be partially buried in the fat of the mons pubis. Very often the penis and testes are extremely small, while the scrotum is so badly developed as to be almost absent ; in fact the whole organ is often not so well formed as in an infant a few months old. Much care has to be taken in these cases before deciding that the testes are imperfectly descended. No boy would be included among our cases in this syndrome who showed normal genital development unless there were other unmistakable endocrine signs and symptoms, but we have placed four boys in this group as constituting links in the chain of this syndrome, most nearly approaching the normal.

The diagnosis in girls is more difficult, but a careful review of the case in the light of the characteristics described in the preceding sections will determine whether there is sufficient evidence for it to be justified. It is not necessary to review the characteristics here, which have all been fully described, except to contradict a statement that pituitary obesity cannot itself be distinguished from obesity due to over-eating. A glance at the plates illustrating this chapter will suffice to show that the children's appearance is far from normal. The fat is excessive, it is found mostly on the trunk and particularly around the pelvic girdle, while in some cases the limbs are entirely normal. These generalisations do not refer to infants, who are not infrequently over-fed and develop obesity from that cause. If over-feeding is absent, then obesity in the infantile years is as strong evidence of endocrine disorder as it is at a later period.

Of other endocrine diseases the only one likely to be confused with this syndrome is thyro-pituitarism. This syndrome, to be described next, resembles pituitary obesity, except that the thyroid plays a much more prominent part. The children have a history of slow mental and physical development. They are late in walking, talking, and cutting their teeth ; growth is slow and epiphyseal development has usually remained below normal. Physically they resemble pituitary obesity in under-development of the sexual organs

and in obesity, which is, however, more generally distributed. Thyroid extract has more effect in these cases, but the general therapeutic response is not so good, because it is not possible to compensate fully for the early thyroid defect. These cases form only a small group compared with the pituitary obesity type, in which thyroid influence plays little part. Pende (3) has recently described a syndrome with the following characteristics. The children are tall and show adiposity of matronly distribution; large breasts are present, but the genital organs are under-developed and the changes of puberty are delayed or absent. The facies is round and childish, with large upper central incisors. Laxity of ligaments causes genu valgum and flat-foot. There are an increase of adenoid tissue and a congenital hypertrophy of the spleen. A somewhat childish emotional reaction is associated with normal intelligence. Investigations show a low blood-sugar and B.M.R., and a high blood-pressure. In Pende's opinion the condition is due to constitutional hyperfunction and hypertrophy of the thymus. This anomaly is difficult to detect by radiography but can be shown with success by deep percussion of the thymus. This account corresponds very closely to our description of the hyperpituitary type of pituitary adiposity, in which excess of growth hormone accounts for the abnormal height and the large size of the teeth. The evidence of thymus involvement appears inconclusive.

Prognosis

Before discussing this question we will state again our hypothesis on the cause of the syndrome. We consider it a variation of the normal physiology of the pituitary gland in which the growth hormone, the gonadotropic hormone, and the mechanism governing the deposition of fats are upset. The latter may be due to disorder of the pituitary-pancreatic balance or the hypothalamus may be involved. Cases vary much in degree. Obesity is the most constant feature, the growth hormone being in excess in most cases and the gonadotropic hormone diminished in most of the boys and some of the girls, while in the girls who mature

early it is possibly in excess. Perhaps these last cases should be put into a special group. The prognosis must depend very largely on the degree of variation from the normal and must differ in each case, especially as endocrine activity may be depressed by some temporary condition from which spontaneous recovery may take place.

Let us consider first the case of boys at or near the age of puberty who furnish complete examples of the syndrome. Case No. 10, reported on p. 66, is a good example. Some children's physicians state that all or most of these cases clear up spontaneously at puberty and class them under such headings as "juvenile obesity" or "familial obesity". We agree that complete recovery in a severe case without treatment may occur. A larger number make a recovery which upon superficial examination may pass as complete; for example, the genital organs may enlarge almost to normal and the adiposity decrease so that in ordinary clothes nothing appears to be wrong. But careful examination will show some abnormality, such as a pelvic girdle of fat or absence of hair on the face; and enquiry may reveal a lack of interest in the other sex and the infrequency of erections and emissions. Probably considerable sexual development occurs spontaneously in most cases, but it may be very delayed and the patients generally remain over-weight. We have been impressed with the difficulty of obtaining an absolutely normal result in a severe case. Some cases do not recover at all, and it is quite incorrect to state that the majority of these cases recover spontaneously at puberty. Plate No. 16 has been inserted as an example of this failure.

When the female patients at puberty are considered the prognosis is usually good if menstruation has occurred; but if it has not, some will pass into the group with delayed development, particulars of which are given on p. 81. By the time they have reached adult life most of them have achieved a measure of endocrine balance, but we know from the histories of our adult patients that some will break down later in life at the times of endocrine stress, pregnancy, and the menopause. We have been impressed with the significance of a history of obesity or of abnormal menstruation in

THE "LINE RATION" DIET SCHEME

(One italic type portion added to one heavy type portion = one Line ration)

Carbohydrate Foods (containing Sugar or Starch)		Heavy Type Portions (Protein and Fat)	
Italic Type Portions (10 g. C.)		7½ g. Protein and 15 g. Fat	
	oz.		(or 9 g. Fat)
<i>Flour, Rice, Sago, Tapioca (raw)</i>	3	One Egg and Fat ¼ oz.	(0) oz.
<i>Oatmeal, Biscuit or Toast ; Macaroni or Prunes (dry)</i>	3	Bacon 1 oz.	(lean only)
<i>Bread (all kinds)</i>	2	Ham 1 oz. and Fat ¼ oz.	(0) oz.
<i>Potato, Peas, Broad Beans ; Banana</i>	3	Kipper 1¼ oz. and Fat ½ oz.	(¼)
<i>Parsnips or Prunes (steved) ; Grapes</i>	3	Herring 1 oz. and Fat ¼ oz.	(¼)
<i>Beetroot ; Apple or Pear (raw) ; Dried Apricots</i>	4	Lean Beef or Mutton 1 oz. and Fat ½ oz.	(¼)
<i>or Peaches (steved) ; Ripe Plums</i>	5	Lean Lamb or Veal 1 oz. and Fat ½ oz.	(¼)
<i>Orange (skinned), or Ripe Greenages</i>	6	Lean Pork 1 oz. and Fat ½ oz.	(¼)
<i>Onions, Carrots ; Cherries, Peaches or Gooseberries</i>	7	Chicken or Duck 1 oz. and Fat ½ oz.	(0)
<i>(all ripe)</i>	8	Tongue (tinned or fresh) 1 oz. and Fat ¼ oz.	(¼)
<i>Milk ; Stewing Apples or Pears</i>	10	Liver 1 oz. and Fat ½ oz.	(¼)
<i>Strawberries or Apricots (ripe)</i>	10	Kidney or Tripe 1¼ oz. and Fat ½ oz.	(¼)
<i>Turnips, Leeks, Jerusalem Artichokes</i>	12	Rabbit or Hare ½ oz. and Fat ½ oz.	(0)
<i>Grape-fruit (in skin) ; Blackberries (steved)</i>	12	Cheese ½ oz. and Fat ¼ oz.	(¼)
<i>Brussels Sprouts ; Raspberries or Loganberries (raw)</i>	12	White Fish ; Sweetbreads 1¼ oz. and Fat ½ oz.	(¼)
<i>Red Currants ; Stewing Greenages, Damsons,</i>	14	Sardines 1 oz. and Fat ¼ oz.	(0)
<i>Plums or Apricots</i>		Salmon 1 oz. and Fat ½ oz.	(¼)
<i>Melon (raw) ; Endive (raw)</i>		Crab or Lobster 1½ oz. and Fat ½ oz.	(¼)
		Pheasant, Grouse, Partridge ¾ oz. and Fat ½ oz.	(¼)

Fats are Meat Fats, Suet, Dripping, Butter, Margarine,
Olive Oil ; Thick Cream in twice the amount stated for
other fats.

* Half portions of these are usually enough.

Negligible Starch Content in Average Helpings of—
Asparagus, Green Artichokes, French Beans, Cabbage, Cauliflower, Celery, Cranberries, Cress, Cucumber, Black Currants, Egg Plant, Stewing Gooseberries, Greens, Horseradish, Lemons, Lettuce, Marrow, Mushrooms, Radishes, Rhubarb, Subsisy, Sweet Runners, Sea Kale, Spinach, Tomato (raw or cooked).

childhood when considering endocrine disease in women. Plates No. 15 and 15A have been included as examples. The prognosis in younger children is more difficult to assess because the degree of gonadotropic deficiency is less clear, and this refers particularly to girls.

Scheme of Treatment

Dietetic treatment.—There are two main objects in treatment, the reduction of weight and the stimulation of sexual development. The first object can be effected by dieting. It is not necessary or desirable to use a starvation diet or a diet composed of protein and fruit only, because it is difficult to maintain an abnormal diet indefinitely, and if the body becomes accustomed to it, an increase of weight is likely as soon as it is changed. The simplest method is to use Lawrence's (4) line diet as prescribed for diabetics. In this scheme food is divided into two sections, one consisting of carbohydrate, the other of protein and fat. Rations are prescribed as so many "lines", a line consisting of a carbohydrate half-line together with a protein and fat half-line. Each carbohydrate half-line contains 10 g. of carbohydrate, and each protein and fat half-line contains $7\frac{1}{2}$ g. of protein and 15 g. of fat. Each line is equivalent to 210 calories, so that it is extremely simple to prescribe a diet of known calorie value and composition. These values have been worked out so that a balanced diet is obtained with sufficient carbohydrate to avoid ketosis but containing much less starch than is found in an ordinary mixed diet. Some vegetables containing very little starch have been listed, and these can be taken over and above the number of prescribed lines; nothing else is allowed except drinks such as tea and coffee, and at the mother's discretion, an occasional sweet or chocolate and some sugar with such articles as stewed fruit. The use of saccharin as a substitute is recommended.

Table A shows the caloric requirements of children at different ages, and with the aid of Table B this can be translated quickly into lines and a diet prescribed. For example, a girl 5 years old weighed 55 lb., which was 13 lb. above the

maximum for the normal child; at that age her caloric requirements are 70 calories per kilogram, according to Table A. To provide that value 55 $6 \cdot 6 = 8$ lines is necessary, according to Table B. But she was much above weight, therefore 6 lines was prescribed, which is a little below the value necessary to maintain her weight at 55 - 13 = 42 lb.

TABLE A

TOTAL CALORIE AND PROTEIN REQUIREMENT OF NORMAL CHILDREN PER KILOGRAM OF BODY WEIGHT

Age	Calories per kg.	Protein g. per kg.
Under 1 year	100	4
1-2 years	90-80	4
2-5 "	80-70	3
6-9 "	70-60	2½
10-13 "	60-50	2
14-17 "	50-40	2-1½

TABLE B

FACTORS FOR THE LINE RATION SCHEME

To obtain Number of Lines containing—	Divide Weight in kg. by—	or divide Weight in lb. by—
20 calories per kilogram	10·5	23·0
25 " "	8·4	18·5
30 " "	7·0	15·4
35 " "	6·0	13·2
40 " "	5·2	11·2
50 " "	4·2	9·0
60 " "	3·5	7·7
70 " "	3·0	6·6
80 " "	2·6	5·7
100 " "	2·1	4·6

Nine months later without other treatment her weight had dropped to 49 lb., while she had grown 1½ in. and increased her span by 2 in. In small children we give diets containing about 60 per cent of the theoretical caloric requirements for their weight; in older children we give diets of relatively lower caloric value. For example, a girl of 16½ years weighed 210 lb., which was 84 lb. above the normal maximum. At 40 calories per kilogram (Table A) she would require 19 lines

(Table B), but she was given 9 lines, which is one line less than is required to maintain the maximum normal for her age (116 lb.). In nine months she had lost 64 lb., grown slightly, and improved in health. It is necessary to maintain the diet indefinitely in most cases, adding to it from time to time as the child grows. The metabolism of these children is so economical that any relaxation leads to rapid increase of weight; but, on the other hand, their economy becomes used to the reduction of starchy food, so that the initial feeling of hunger soon wears off. We have watched children on this diet for as long as nine years, and it is satisfactory in every respect. The success of the diet in reducing weight depends on the strictness with which the mother follows instructions; when these have been properly carried out, we have never failed to obtain a reduction. But it should be emphasised that it is useless to give general instructions to reduce starchy food, for these are either disregarded or an unbalanced diet is given.¹

Endocrine treatment.—Before describing the treatment of pituitary obesity it is convenient at this point to say a few words about endocrine treatment in general. With the exception of the use of thyroid gland, and despite the recent advances which have led to the chemical preparation of a number of hormones, the action and composition of many of the substances which we use are only partly known, the dosage and duration of treatment are in the experimental stage, and possible complications, such as anti-hormone action, are not properly understood. Whenever possible, standardised products have been used but it is not possible to avoid altogether the use of crude extracts. Great care is necessary in using endocrine treatment, especially in children. At the same time the syndromes described in this book constitute in many cases such a serious handicap that treatment should be attempted and some slight risk is justifiable. We have erred, if anything, on the side of caution and throughout the book we speak from our own experience unless another reference is given.

¹ At the present time (1942) rationing has made dieting very difficult, but much may still be done if intelligence is used.

We will now consider the treatment of pituitary obesity in detail. Dietetic treatment is used as a routine measure in all cases, endocrine treatment being adjusted to the individual patient. It is convenient to consider the method of treatment by age groups and to take the youngest patients aged 3 to 10 years first; they are all given routine dietetic treatment and weighed regularly. When no further reduction can be obtained, thyroid gland is added in doses of $\frac{1}{4}$ to $\frac{1}{2}$ gr. of Burroughs Wellcome's fresh thyroid gland twice daily, and this is increased up to the maximal tolerance of the patient, i.e. until the pulse and rectal temperature are raised and the child becomes fretful. The dose is then reduced to about two-thirds of the maximum and continued for some weeks to note the effect; if improvement does not occur, thyroid gland is discontinued. Thyroid gland does not benefit the majority of the children, but there are a few who consistently lose weight when it is given and gain weight when it is omitted. There is a considerable number of children who will tolerate large doses without deriving any benefit; in those patients it should not be given. In this age group we do not as a routine give any endocrine treatment other than thyroid gland, unless some special symptom demands attention. Diabetes insipidus, pronounced sleepiness, excessive hunger, fits or mental dullness associated with a recent increase of weight would justify trying a pituitary preparation. Diabetes insipidus should be treated with posterior pituitary snuff, the other symptoms with whole pituitary powder intranasally or injections of whole pituitary extract. A good effect on these symptoms is often obtained and the mother frequently reports mental improvement.

It has been argued that the use of pituitary gland in this syndrome is not justified on the following grounds: that the abnormally rapid growth of the children shows that there is no pituitary deficiency; that the obesity is entirely a hypothalamic syndrome and would be unaffected by pituitary therapy; that there is no evidence that pituitary therapy influences obesity from any cause. Such arguments overlook the dissociation of pituitary functions that occurs in this syndrome, the intimate connection between the hypothalamus

and the pituitary gland (see Chapter 6), and our ignorance of the exact cause of the obesity which may well involve the anterior lobe as well as the hypothalamic-pituitary mechanism. For these reasons we think that the use of pituitary preparations is justified in some cases.

Pituitary preparations are destroyed when given by mouth, and we never prescribe them by this route ; but the alternative of injecting preparations into small children over long periods is unsatisfactory. Instead of injection we have given both anterior and posterior pituitary powder by nasal insufflation. This method has been used for some time in the treatment of diabetes insipidus with posterior pituitary substance sometimes with great success (see p. 269), and experience in this disorder led us to try the same method in other conditions and to use anterior pituitary powder as well. We think that a physiological effect can be obtained in this way as shown by the stimulation of sex development in boys, but we are unable to give the experimental evidence which is desirable before anterior pituitary powder is generally used in this way. The instructions we give are as follows. The child is to lie on a couch, and a small quantity of the powder is to be brushed inside each nostril twice a day with a camel's-hair brush. The brush must be washed and dried after each dose or it becomes hard and useless. In practice, at first about a grain of powder is taken a day, but this may be increased. In older children the powder may sometimes be taken better by putting a small portion on the hand and snuffing it up the nose. We have used powder prepared by Messrs. Armour and during the last few years by Messrs. Paines and Byrne, who have kindly supplied the following information respecting the mode of preparation of the pituitary powder : " All glands are obtained from cattle killed for human consumption and are removed immediately after slaughter and placed in preserving fluid. They are then stored in a refrigerator until a sufficient quantity has been collected for processing and subsequently dried *in vacuo* at a low temperature. The resulting product is a dry powder of either anterior or posterior pituitary lobe with a high physiological activity."

Now we come to the next age group, 11 to 14 years. Many children's specialists maintain that there is no necessity to give endocrine treatment even to the boys, because normal development will eventually take place. We have expressed our views on this outlook in the preceding pages and we think that every effort should be made to initiate normal puberty changes during this period, especially in those patients who show imperfect descent of the testes. In this last group we give at once one of the pregnancy urine preparations of pituitary-like hormone, which are gonadotropic. There are many preparations, but we have only had extensive experience of two: Antuitrin S. (Parke Davis) and Pregnyl (Organon). They contain for the most part the luteinising factor and therefore act predominantly upon the connective tissue derivatives, the theca cells of the ovaries, and upon the interstitial cells of the testes leading to increased internal secretion. Both preparations are effective in stimulation of sexual development in the male. They are used in doses of 200-500 rat units three times weekly for two months. If the result is not satisfactory we repeat the same doses after a two-months interval. If little improvement is obtained, we wait and give further treatment between the ages of 13 and 14 years. At that time if genital development is very backward we give an intensive course consisting of 200 rat units of gonadotropic substance daily for one month.

We also use injections of more crude extracts of anterior pituitary gland and whole pituitary gland. The former preparation would be appropriate, for instance, where the child is generally under-developed, and the latter where some special evidence of posterior lobe or hypothalamic involvement such as excessive water intake is present. We have used preparations made by Paines and Byrne, who have supplied the following note on these preparations: "The anterior and whole gland pituitary extracts are not standardised on their hormone content but are total extracts. It is generally considered that the gonadotropic hormone predominates in the anterior pituitary extract, and small amounts of the growth and lactogenic hormone are also present. The whole pituitary preparation would contain the

above hormones and, in addition, the oxytocic and pressor hormones of the posterior pituitary gland. Because of its known effect in certain types of obesity it is suggested that the latter preparation also contains the carbohydrate metabolising hormone." The doses of anterior pituitary gland vary from gr. xv to gr. xxx from two to three times a week to once a day, whole pituitary gland in doses of gr. v to gr. x daily or two or three times a week, both given in courses of two or three months followed by an interval of several months without injection. If small stature is a prominent feature, which is unusual in this syndrome, Antuitrin G. (Parke Davis) may be given. This is a preparation containing a high proportion of growth-stimulating factor and should be given in doses of not less than 5 c.cm. twice weekly. Further particulars in the use of this preparation will be found in Chapter 6. Careful watch is kept on the girls, and if there are no signs of development towards the end of this age period we give preparations containing a follicle-stimulating hormone, such as Gonadotraphon (Paines and Byrne), which is derived from the anterior pituitary gland itself and contains in addition a luteinising hormone. A course of 200-500 rat units three times a week is given for a month and after a few weeks is repeated. In the past we have used pregnancy urine preparations in the girls, but as these are now considered to be ineffective in stimulating the ovarian follicle, we have largely ceased to use them, though the results at the time appeared encouraging.

Boys seen after the age of 14 years with much under-development are given intensive treatment. This consists of courses of the pregnancy urine preparations (Pregnyl and Antuitrin S.). If puberty changes are not evident after the age of $14\frac{1}{2}$ years in the girls, we have been using lately a follicle-stimulating preparation from pregnant mares' serum (Serogan). A dose of 200 i.u. of Serogan should be given twice weekly for two weeks, followed by a luteinising preparation such as Pregnyl, 500 rat units twice weekly for one week. After a week's rest this routine is repeated several times, the dose of Serogan being increased to 1000 units if no effect is produced. We have not had sufficient experience

yet to know whether much improved results will follow.

At 14 years and after, a secondary hypothyroidism due to lack of pituitary gonadotropic hormone may be present, in which case thyroid gland should be given to the limit of tolerance of the patient. No mention has been made of ovarian or testicular hormones; they are seldom required, for they do not give the necessary stimulus to the sex organs, acting for the most part on the accessory organs of generation. These preparations find a place, however, in the treatment of the adolescent patient whose genital development remains subnormal despite intensive treatment with gonadotropic preparations. This type of patient should be treated on the lines suggested in Chapter 8.

To conclude this section there are a few general points to mention. All the above preparations may be used without fear of immediate unpleasant reaction with the following exceptions:

- (1) Preparations of posterior pituitary gland occasionally cause abdominal pain and consequent faintness, and therefore it is wise to prescribe a small initial dose.
- (2) Very rarely an idiosyncrasy to the pregnancy urine preparations is present, producing local swelling and pain not of a serious nature but sufficient to prevent their use in a child.
- (3) A mild nasal catarrh sometimes results from the use of pituitary snuff.
- (4) When menstrual function has been started by treatment, continuous bleeding sometimes occurs. This should be treated with corpus luteum hormone 1 i.u. daily for a week, or raising the oestrin level with small doses of stilboestrol may be effective. This complication is not common, and we have not seen a case so severe as to cause anxiety.

Results of treatment.—The assessment of the results of treatment in children is very difficult because of the natural growth and development. We have paid great attention to this question for ten years but we are not prepared to make many definite statements. Our main purpose will have

been achieved if we arouse sufficient interest to rescue this syndrome from neglect, when ample evidence of the effect of treatment will in time be accumulated. One or two general statements can be made.

OBESITY.—There is no doubt of the great value of dieting as described in this chapter. Under controlled conditions we have never failed to obtain a reduction of weight independent of any hormone therapy, but results in out-patients are often disappointing. The benefit of a large reduction of weight, as shown in the plates illustrating this section, cannot be exaggerated. It is sometimes said that, as many of these children would lose weight at puberty, strict dieting is unnecessary. On the contrary, if it were true that every one of them became quite normal at puberty, it would still be worth while to diet them strictly because improvement can be obtained quickly. A reduction of weight, as shown in the plates, completely alters the physical capacity of the child and may have a correspondingly good effect on the mental outlook. The resulting increased skill at games is an important factor in the happiness of the girls as well as the boys. Dietary restrictions have to be maintained in some cases into adult life, or an immediate gain of weight occurs, but some patients become able in adolescence to take a normal diet. Many patients of both sexes remain somewhat over-weight. We have no conclusive evidence that pituitary preparations cause a loss of weight. We have never seen any untoward symptoms from a rapid reduction of weight, such as the syncope, weakness, hypoglycaemia, and anorexia which are described by some writers (5).

GENITAL UNDER-DEVELOPMENT.—We have no doubt that treatment as outlined above stimulates sexual development. We think that this treatment should be undertaken so as to initiate the changes of puberty at about normal time. How much development would take place without treatment it is impossible to know, but we think that the histories of adult endocrine patients in the future may put the matter beyond doubt, and show the importance of diagnosis and treatment in childhood.

Conclusion

Childhood pituitary obesity has been dealt with at length for the following reasons :

It is the most common endocrine disorder in childhood, it is frequently neglected when the signs are obvious, and in its lesser degrees it is entirely disregarded. When it is recognised it is usually thought to be due to neoplasm ; but on the contrary this is scarcely ever the case, and the hypothesis is advanced that it is due to pituitary imbalance probably with hypothalamic involvement.

Treatment is beneficial, and the best results are obtained in cases in which treatment is instituted before the normal age of puberty.

Neglect of the syndrome leads in many cases to pathological obesity and in some cases to defective sexual development. These defects may persist throughout life, and in women are the cause of many cases of menstrual disturbances and of endocrine disorder after childbirth. In men sexual under-development occasions much distress, and in both sexes we think this syndrome to be one of the causes of premature senility.

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Thyro-pituitarism

In the preceding section it has been emphasised that pituitary obesity is due to disorder of the pituitary-hypothalamic mechanism. There is no evidence of primary thyroid gland involvement because the mental and physical development in infancy is not retarded, the epiphyseal development is normal or advanced, and thyroid gland does

little good. These facts are true of the clear-cut syndrome, but there are a number of cases in which there is some evidence of thyroid defect, shown by a response to thyroid medication, or some retardation of epiphyseal development. Where thyroid defect is slight the cases are classified under the heading of pituitary obesity, but where the defect is sufficiently pronounced to cause delayed development in infancy, they are classified under the heading of thyro-pituitarism. These cases shade into one another by small variations so that a series of cases can be found to bridge the gap between pituitary obesity and thyro-pituitarism.

Characteristics of Thyro-pituitarism

This is a far less numerous group than pituitary obesity. The thyroid defect is congenital, and since the thyroid is concerned with differentiation of tissues, development both physical and mental is delayed, so that teething, walking, and talking take place late and there is delay in the appearance of the epiphyseal centres. The birth weight may be above normal owing to hypothyroidism, but in many cases birth is premature and the child is undersized, probably owing to prenatal inactivity of the anterior pituitary lobe, for the pituitary defect may either be congenital or else induced by infection at a later date (see p. 100). A family history of endocrine disease is found, as in pituitary obesity, and the general appearance of the child resembles that group, but the fat is more generally distributed and may show some of the characteristics of hypothyroidism such as pads above the clavicles. The skin may be dry and the hair coarse and lacking sheen. The stature depends on the balance between the thyroid and pituitary factors, but, unlike the pituitary group, is usually below normal. The face is fat, often cretinoid and stupid, contrasting with the alert expression of the pituitary patient. Internal strabismus is often present. The genital organs are usually underdeveloped and undescended testes are common. The teeth may show characteristics of hypothyroidism such as overcrowding, or may be influenced by pituitary factors and show wide separation. The B.M.R. is below normal. Mental

defect usually persists in some degree. Most of the points are exemplified in the following case histories.

CASE NO. 48.—A boy aged 7 years and 10 months. Thyroid disease is present on both sides of the family. The parents are of opposite types, the father being very tall and thin, the mother short and stout. Walking and talking were delayed, but nothing else abnormal was noticed until after an infection, diagnosed as glandular fever, at the age of 5 years, after which he became very fat. Thyroid gland treatment led to some improvement. When he first came under observation three years later, he showed adiposity of the trunk and thighs and some fatness of the face, and he weighed 84 lb., 26 lb. above the normal maximum for his age. His movements were slow and he was clumsy with his hands, and mentally very backward. The penis, scrotum, and testes were small. When treatment with anterior and posterior pituitary powder was given, as well as thyroid gland, a considerable mental improvement was at once noticed at school, and he began to lose weight. No change was made in his diet, for the parents had always restricted the use of carbohydrate. A year later the weight had come down to 74 lb., the chest measurement had decreased by $1\frac{3}{4}$ in., and the abdominal measurement by 3 in. The pituitary powder was continued for two and a half years and the patient grew 4 in., but the weight rose to 91 lb., 16 lb. above the normal maximum. Since he was now $10\frac{1}{2}$ years old and no improvement in the genital organs had taken place, Pregnyl was given in a dose of 500 rat units twice weekly. After the third week of treatment erections occurred with much local irritation, followed by rapid genital growth and development of the pubic hair. In three months the genital organs had nearly reached normal size, and treatment with Pregnyl was stopped. When last seen, $11\frac{1}{2}$ years old, the weight was 112 lb., which is 29 lb. above the normal maximum, but he was much better proportioned. The penis and testes had continued to develop normally under treatment with thyroid and pituitary powder. He was about two years behind in school work, but this represented a great improvement compared with the period before pituitary treatment had been given.

CASE NO. 46.—A boy first seen aged 4 years, who has been followed for fifteen years. He is said to have been a full-time baby but only weighed 6 lb. The teeth were cut early, but he did not walk until he was 3 years old. After saying a few words at 12 months he invented a language of his own and at 4 years could not speak properly, although he appeared to understand what was said. *On examination*, the patient showed some adi-

posity, with a pelvic girdle. The face was fat and the expression stupid, the appearance of the eyes was cretinoid with a slight left internal strabismus, the hands were stumpy and the genital organs small. He appeared abnormally excitable. Treatment by diet and thyroid gland was given for a year with some improvement, then he ceased attendance for eight years, when he reappeared aged $12\frac{1}{2}$ years. He was still fat, 20 lb. above the normal maximum, and the genital organs remained small. The mental defect persisted, speech was slow and slurred, and nystagmus was present. Pituitary powder was given, and after five months the genital organs had enlarged to normal and some improvement was noticed at school. The powder was continued for two years with some mental improvement, but he remained very much overweight. It was noticed that he became nervous and that speech was more difficult to understand whenever the powder was omitted. He was seen again at the age of $15\frac{1}{2}$ years when treatment had not been given for a year. He could read and add up quickly, but his reasoning power was very poor and the physical condition had not altered. By the age of 19 years a striking change had taken place, as he had aged so much that he looked more than twice his age. Almost all fat had gone, and he was entirely bald except for a little hair on the side of his head; he moved slowly and deliberately, and when bicycling the action resembled a man of 65 years. He was a striking example of the ageing effect of endocrine disease.

CASE NO. 45.—A boy aged 11 years. The father was mentally abnormal, and one elder brother was of a similar type to the patient. He had been a premature breech delivery, weighing only 6 lb. at birth, and trouble was experienced in rearing him for he was late in teething, walking, and talking. At an early age he became fat and when seen at the age of 11 years he weighed 108 lb., which is 27 lb. above the normal maximum. The genital organs were under-developed, but mental development had been normal. He was treated with thyroid gland and Pregnyl, 500 rat units twice weekly for six months, followed by anterior and posterior pituitary powder for five months. The result was very satisfactory; the general appearance became almost normal and the genital development quite normal, no further treatment being required.

The first two cases described are typical of this group; in the first there was a family history of thyroid disease. Both boys showed typical delay in early development, and neither became mentally normal even after prolonged

treatment, although both were greatly benefited in physical health and genital development. The third case illustrates the importance of looking for minor degrees of this syndrome, for treatment was successful in producing an almost normal child. Radiographic examinations were not available in these cases.

Diagnosis, Prognosis, and Treatment

It is plain that thyro-pituitarism forms a link between childhood pituitary obesity and hypothyroidism ; it merges into the former and some patients are classified with difficulty. The evidence for thyroid gland defect is provided by the history of retarded mental development, delay in appearance of the centres of ossification, and a greater response to thyroid gland treatment than is obtained in pituitary obesity. Physical development also may be retarded and considerable difficulty experienced in feeding during infancy. On the other hand, the typical pituitary patient shows normal or advanced mental and epiphyseal development.

The B.M.R. is reduced in thyro-pituitarism, but this cannot be used in distinguishing the two conditions because it is also frequently lowered in pituitary obesity (p. 83), even when there is no other evidence of thyroid gland defect. We have not made the diagnosis of thyro-pituitarism unless there was a history of retarded development, thus giving clear evidence of congenital hypothyroidism ; if this criterion is maintained, most of the doubtful cases fall into the pituitary group.

From the hypothyroid or cretinoid cases the distinction again is one of degree. The typical cretin shows a far greater degree of thyroid defect, leading to extreme retardation of development both mental and physical. The characteristics which are described under hypothyroidism are distinctive (see Chapter 10).

The outlook is not nearly so good in thyro-pituitarism as in the pituitary group. The congenital thyroid defect is an additional handicap which cannot be completely relieved by treatment. In the less severe cases, particularly when

mental faculties are not much disturbed, much benefit may result from treatment, as in the third case quoted above, but in the majority mental defect persists.

The above descriptions of several case histories show that treatment is on the same lines as in the pituitary group, except that thyroid gland is given in large doses to the maximal tolerance of the patient and maintained indefinitely in most cases.

CHAPTER 5

HYPOPITUITARISM

Anterior Lobe Hypopituitarism (Primary Growth Hormone Deficiency)

(*Synonyms* : pituitary infantilism, Lorain-Levi disorder, ateleiosis)

IN 1908 Levi described a girl of 20 who was only 4 ft. 4 in. high and sexually under-developed with ununited epiphyses and an enlarged pituitary fossa presumably due to pituitary tumour. This syndrome of arrested growth and sexual development associated with poor muscular development and without adiposity became known as the Lorain-Levi syndrome. Hastings Gilford (1) described the same condition when writing on disorders of growth under the name of ateleiosis. As in Levi's case, tumour formation in the pituitary gland, or pressure from a suprasellar tumour, may impair the function of the anterior lobe and produce the syndrome. In our series of cases tumour was not present and we are concerned in this chapter with an impairment of function not associated with new growth. The Lorain-Levi syndrome and ateleiosis can now be grouped under one heading and are known to be caused by defective secretion from the pituitary anterior lobe. The growth hormone is most deficient, but the gonadotropic hormone is affected also, because in most cases sexual development remains infantile. Anterior lobe hypopituitarism is the opposite of anterior lobe hyperpituitarism and an interesting contrast is provided by the patients in Plates No. 19 and 20. It causes retardation or arrest of growth of the whole body, including the brain and the internal organs. The onset of this condition may occur spontaneously, following infection, or,

more usually, very slow growth is present from birth. Hastings Gilford recognised the juvenile cases, but for the most part they have been overlooked and only the extreme forms have been noticed after puberty. We wish to emphasise the importance of considering the possibility of this syndrome in small under-weight children who show no signs of non-endocrine disease. The diagnosis can be made by comparing the growth increment of the patient with the normal and affords yet another example of the value of routine measurements in childhood. The preparation of pituitary growth hormone in relatively pure form aroused great interest and gave a hope of therapy, in this condition. Up to the present the results of treatment have varied considerably, although some striking results have been obtained. Our experience is encouraging but we hope for better results in the future. It is naturally very difficult to prove the effect of treatment on growth in a child, but in the following case we have approached very closely to experimental conditions.

CASE No. 61.—Plates No. 17 and 18. A girl aged 16 years. She had nine normal brothers and sisters, and was brought up under the same conditions. Her birth weight was $8\frac{1}{2}$ lb. She progressed normally until 9 months old, when she had a febrile illness and thereafter grew very slowly and did not walk until she was 2 years and 2 months old. Mental development was much retarded, and growth ceased at about 6 years of age. Thyroid gr. $\frac{1}{2}$ T.D.S. was then given for two years, with, it is said, some benefit to weight and mentality, but she had no further treatment until she came to hospital at the age of 16 with a history of ten years' arrested growth. Photographs taken when she was 6 years old and compared with her appearance ten years later confirmed this statement.

On examination, December 16, 1933, she was the average size of a child between 5 and 6 years old. The upper measurement was 2 in. longer than the lower, the span and height were equal. There was very little subcutaneous fat and no pads of fat. The skin could be lifted up loosely as in an old person, and it was dry, hard, and wrinkled, resembling a mild degree of ichthyosis. The complexion was sallow. There had been one menstrual period at the age of 12 years. She had reached Standard IV at school at 13 years. The sigma reaction was negative. The blood chemistry and urine were normal. The visual fields

were normal. The development of the epiphyses corresponded to a child of 6 years old. The pituitary fossa was slightly large. The dentition was much delayed.

Treatment.—She was given a small dose of thyroid and Antuitrin (Parke Davis) 1 c.cm. daily for eight months. Immediately there was a remarkable effect on the skin, which rapidly became normal. At the end of nine months she had grown $3\frac{1}{2}$ in. and

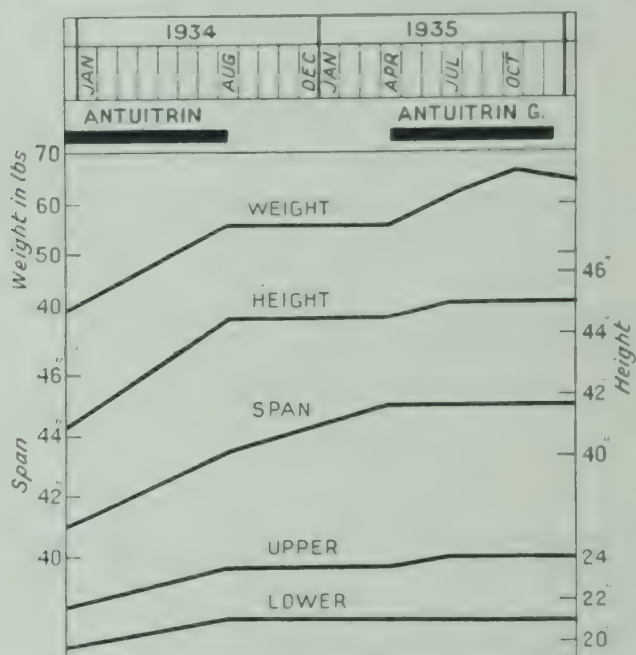


FIG. 3.—Case No. 61 illustrating action of growth hormone on development.

gained $16\frac{1}{2}$ lb., nearly a 50 per cent increase in weight (see Fig. 3). In order to show that this growth was due to treatment, it was omitted for nine months, and during that time development practically ceased. Treatment was then recommenced with Antuitrin G. 1 c.cm. daily (a purer preparation of growth hormone which had come on the market in the meantime), and development began again to some extent, although the patient was then over 17 years old. After a further eight months no improvement could be obtained and treatment was stopped. When it is remembered that this child had not grown for ten years before treatment, it can hardly be doubted that the pituitary growth factor was responsible. Plate No. 18 shows the patient after treatment at the age of 18 years. In May and August 1935 menstrual periods occurred. From September 19 to December 19, 1935, 250,000 units of Progynon B Oleosum were given twice weekly. No effect on menstruation was observed. We are

indebted to Mr. Baxter for the following note on September 6, 1935: "The uterus corresponds in size to the size of the individual and a sound entered $11\frac{1}{2}$ inches. An injection of lipiodol demonstrated that the uterine cavity was cylindrical in shape." After the above treatment with Progynon B Oleosum, a triangular cavity was demonstrated by lipiodol examination by Mr. Baxter, and the uterus was shown to have increased in size considerably.

A year after she had first come under observation, re-examination of the epiphyses showed that the ossification now corresponded to her age. Treatment had caused ten years' advance to occur in one year. This case was complicated by a grave defect in mentality which is not usual in pure hypopituitarism and occurred only in one other case. While under treatment with growth hormone, the patient on a number of occasions became semicomatose for some hours. Treatment was temporarily omitted and recovery ensued. We were unable to account for this symptom at the time but possibly hypoglycaemia was the cause.

Case No. 61	Age 16	Normal Child age 5	Age 16 years 8 Months	Age 18
Head . .	20.5 in.	20.0 in.	21.25 in.	21.25 in.
Chest . .	22.0 "	21.4 "	25.0 "	27.5 "
Abdomen .	21.5 "	19.9 "	26.0 "	27.0 "
Height . .	41.0 "	40.75 "	44.5 "	45.0 "
Lower M. .	19.5 "	19.25 "	21.0 "	21.0 "
Upper M. .	21.5 "	21.5 "	23.5 "	24.0 "
Span . .	41.0 "	39.2 "	43.25 "	45.0 "
Weight . .	39.0 lb.	33.8 lb.	55.5 lb.	64.5 lb.

The result of treatment in this case convinced us that growth could be stimulated by pituitary preparations and caused us to attach more importance to the results obtained in other patients, in which facts were not so clear-cut.

CASE No. 105.—Plate No. 14. A girl aged 14 years. The mother is small but the height is within the normal range. Although there are seven other children of normal size in the family, the patient grew slowly from birth, as can be seen by the following measurements which were kindly given to us from the records of the school medical service of Berkshire.

Case No. 105	Age		
	5 Years 7 Months	8 Years 8 Months	12 Years 4 Months
Height . .	35 in.	40 in.	46 in.
Weight . .	29 lb.	36 lb.	57 lb.

These show that the height for the age of $5\frac{1}{2}$ years was about 10 in. below the mean normal figure, while the weight was correspondingly low.

For a year before coming to hospital she had suffered from headache and bilious attacks and had fainted several times for no reason. At school her work was about the average for her age. *On examination* she was very small, as can be seen in Plate No. 14, where she is compared with a sister three years younger. Menstrual periods had not started. The table shows the measurements during the period of observation. She was no less than 11 in. shorter than the normal minimum and 30 lb. below the minimal weight.

Case No. 105	Age				
	13 $\frac{1}{2}$ Yrs.	14 $\frac{1}{2}$ Yrs.	14 $\frac{1}{2}$ Yrs.	15 $\frac{1}{2}$ Yrs.	16 Yrs.
Head .	20.0 in.	20.5 in.	20.5 in.	20.5 in.	20.5 in.
Chest .	28.0 "	28.0 "	28.0 "	28.5 "	29.0 "
Abdomen .	26.5 "	27.0 "	26.0 "	25.0 "	27.0 "
Span .	50.0 "	51.0 "	51.0 "	53.0 "	53.0 "
Height .	47.5 "	48.5 "	49.25 "	51.0 "	51.75 "
Lower M. .	25.0 "	26.0 "	26.0 "	26.75 "	27.25 "
Upper M. .	22.5 "	22.5 "	23.25 "	24.25 "	24.5 "
Weight .	59.0 lb.	65.0 lb.	69.0 lb.	70.0 lb.	74.0 lb.

She differs from the typical picture of anterior hypopituitarism in showing adiposity, probably indicating that the hypothalamic-hypophyseal mechanism is deranged in addition to the anterior lobe growth hormone defect. For this reason she would possibly be more correctly classified under childhood pituitary obesity, in the small group of those cases which show growth defect; however, the case is described here to show the link between the two conditions and to emphasise the intimate relationship between these pituitary syndromes. Investigations showed a negative sigma reaction, a B.M.R. of -12 was just below the minimum normal and a rather high cholesterol in the serum, 221 mg. per cent. Radiographic examination of the skull was normal and the epiphyses showed slight retardation.

The table of measurements shows her development during the next two years. Because of the association of adiposity with small stature she was given injections of whole pituitary gland twice weekly for five months, doses were first gr. v, then gr. x, and finally gr. xv. Immediately on starting treatment, the symptoms of biliousness and headache disappeared, and within three months she grew 1 in. in height and during the following two months a further $\frac{3}{4}$ in. was added. This remarkable result,

which coincided with a great improvement in general health and appearance, is not likely to have been a coincidence. After this spurt growth became slower and during the next year she grew $1\frac{3}{4}$ in. During that year the whole pituitary gland injections were continued for two months, making seven months in all, and Antuitrin G. 2 c.cm. twice weekly was added during two months, then all injections were stopped and anterior and posterior pituitary powder was substituted for six months, thyroid gland gr. i B.D. being taken throughout the period of treatment. She was now 15 years and 3 months old and a further course of Antuitrin G, consisting of 1 c.cm. three times weekly for three months, was given. The question of expense limited the dose, which would otherwise have been much larger. Treatment was then continued with thyroid gland, and just before she became 16 years old the first menstrual period occurred. She remains under treatment but it is not likely that much further growth will be obtained. Unfortunately the patient is still far below the minimum height, but the increase that has been obtained has greatly improved the general appearance, for it will be noted that the chest and abdominal measurements have remained almost unchanged throughout. Radiographic examination of the epiphyses still shows slight retardation.

Growth defect of the severity described in the above two patients is rare and therefore not of itself of great importance. The next case is an example of a less severe type, which is much more common and in which endocrine defect may easily be overlooked, to the detriment of the patient.

CASE No. 50.—A boy aged 16 years. His mother was small and of poor intelligence, and he had always developed slowly, physically and mentally, and was extremely nervous and lacking in confidence for his age. He had suffered severely from attacks of headache and vomiting. The puny development is clearly shown by the measurements, and he had a dull expression not helped by the presence of internal strabismus. The genital development was normal, indicating a clear-cut growth deficiency (Hastings Gilford's (1) sexual ateleiosis). No investigations were carried out. The measurements compared with the normal and contrasted with those taken two years later are shown in table on p. 110.

This boy was given Antuitrin G. 5 c.cm. twice weekly for two years with occasional intermission, together with thyroid gr. $\frac{1}{2}$ B.D. The measurements indicate the great improvement,

Case No. 50	Patient	Normal for 16	M. after 2 Years
Head . . .	21.0 in.	22.0 in.	21.25 in.
Chest . . .	27.0 "	31.7 "	29.0 "
Abdomen . . .	23.0 "	27.2 "	25.75 "
Span . . .	59.5 "	63.4 "	64.0 "
Height . . .	58.0 "	62.0 "	64.25 "
Lower M. . .	30.25 "	32.0 "	34.0 "
Upper M. . .	27.75 "	30.0 "	30.25 "
Weight . . .	69.0 lb.	96.0 lb.	89.0 lb.

6 $\frac{1}{4}$ in. in height and 20 lb. in weight, that occurred, but the gain in confidence and ability was proportionately even greater. Before treatment it seemed unlikely that this boy could ever earn his own living, but afterwards, despite somewhat small size, he appeared quite capable of standing up for himself. No gonadal stimulation was required in this patient. This case emphasises the importance of diagnosing and treating energetically mild examples of this syndrome even when they are seen at a relatively late age.

Symptomatology

These cases illustrate both severe and mild forms of the condition. The very severe form was described by Hastings Gilford as ateleiosis, and most circus dwarfs come within this category or that of achondroplasia. Hastings Gilford (1) divided ateleiosis into a sexual and asexual type, but as in all endocrine disorders infinite variation can be found, and while most of the cases show sexual infantilism and fall into the asexual group, some, like Case No. 50 reported above, have normal sexual development and correspond to the group of sexual ateleiosis.

In our series of hypopituitary cases we did not find the same frequency of endocrine dysfunction in the family history as in the pituitary obesity cases, but the parents or grandparents were noted to be small in a few instances. One of our patients has a sister who is being treated for pituitary obesity. The history of the patient usually shows that slow growth has been present from birth, thus indicating a congenital origin. The intellectual development is usually normal but nervous symptoms are almost always present, either from an early age or developing at the age of puberty.

At that time the persistence of a childish emotional reaction with lack of self-confidence and dependence on others constitutes a severe handicap and may prevent proper progress in any sphere of activity. The lack of the normal aggressive powers is particularly noticeable in boys who are easily imposed upon by younger children. Headache is a frequent complaint, often associated with bilious attacks and an intolerance of fat. These children are often included in the group of under-weight children who are said to be suffering from "acidosis". The appetite is poor and constipation frequently present.

The characteristic signs, deficient growth, poor muscular development, and sexual infantilism, are well illustrated in the cases described above, and other examples are shown in Plates No. 20 to 25. The lack of growth hormone typically results in the upper measurement being relatively long compared with the lower, but this is by no means always the case. All other measurements are uniformly diminished and the bones are small. The teeth are often miniature in size, generally well formed and sometimes widely separated. The skin is fine, thin, smooth, and hairless in the younger children, but in the older cases it is sometimes extremely harsh and dry, as reported in Case No. 61 above. This may be a hypothyroid symptom but it is one of the first things to clear up on treatment, and will do so rapidly with pituitary preparations alone. Susceptibility to fatigue and cold are complaints which may also be of hypothyroid origin. Childish as is the general appearance of the body, this is often in striking contrast to the aged appearance of the face, and this is well illustrated in Plate No. 23. If the body in this illustration is covered the face looks like that of a woman of 25-30 years old, the actual age being about 13, and exemplifies the important fact that all pituitary disorder leads to premature ageing. A delicate wrinkling of the skin of the face is partly responsible for the appearance of age, and although found at times in other pituitary syndromes, is particularly common in this one. The colour of the face is often distinctive, but difficult to describe, giving the patient a pale transparent appearance, the opposite of the plethoric

red complexion found in hyperpituitarism.

Apart from the diminished stature the genital signs are the most important. In the early years there may be nothing to be noticed as the external genitalia are often normal, but at puberty development does not take place at all in the more severe examples. In some patients, however, genital growth takes place and secondary sexual characteristics appear more or less completely, so that we find a variety of cases differing from one another in severity of growth and sex defects.

Hyperextensibility of joints may be found in this, as in childhood pituitary obesity. In the early years there is no epiphyseal abnormality, but later the appearance of the centres is delayed, probably due to a secondary hypothyroidism. These patients remain thin into adult life but we have noticed that obesity may develop at a later date.

Diagnosis

We have to exclude non-endocrine causes divided into two groups :

- (1) Conditions which are probably of genetic origin ;
- (2) Conditions of non-genetic origin ;

and a third group which must be considered is

- (3) Other varieties of endocrine disorder.

(1) *Conditions of genetic origin.*—Families of dwarfs have been described from time to time but these are distinguished by their normal sexual development. Apart from actual dwarfism, small size (without evidence of endocrine disease) may be a characteristic of a family, but is not usually outside the range of normal measurements.

Achondroplasia is a condition which is usually sporadic but may be hereditary. An abnormality of cartilage bone formation arising in foetal life results in deficient growth of the long bones. The general characteristics which are quite distinctive are as follows. The extremities are very short with bowed limbs and large feet, the sacrum is tilted forward giving a prominent abdomen and apparent lordosis. The

head is large, the face small with pug-nose, the hands show fingers of equal length (trident hand). If these children survive the first year, they show a marked virility with a strong muscular system. The sexual development may be normal or infantile.

Microcephaly with mental deficiency is often associated with infantilism, but the diagnosis is clear from the size of the head, not more than 17 in. in circumference, associated with mental defect.

(2) *Conditions of non-genetic origin.*—There are a large number of conditions which may in rare instances be associated with stunted growth and infantilism, tumours of the pituitary or its neighbourhood, any long-standing infective process like syphilis, any abnormality like congenital heart disease, or any chronic nutritional disturbance, may be the cause. In most of these conditions the clinical picture is probably produced by an inhibitory effect on the anterior pituitary gland, but the one in which the underlying condition is likely to be overlooked is the last-mentioned.

The chronic nutritional disturbance is generally of intestinal origin and most frequently coeliac disease is the cause. This condition begins in the infantile or juvenile years with difficulty in absorbing fat, the stools become bulky and contain an excess of fat, growth is stunted; emaciation ensues, and in severe cases sexual development does not occur. Even if the original trouble is cured, a condition of infantilism may persist and the origin be overlooked if careful enquiry is not made. A similar condition in the young adult, either arising spontaneously or as a sequel to the childish complaint, is called idiopathic steatorrhoea, and if it appears sufficiently early may stunt growth and development in the same way (see Plate No. 24). There may be some particular significance in the fact that disturbance of fat absorption is associated with infantilism, for intolerance of fat and bilious attacks are symptoms of hypopituitarism. It certainly is a point in favour of our view that some of the children diagnosed as "cyclical vomiting" and "acidosis" come into this category.

Chronic nephritis in children may cause infantilism as will

hydronephrosis but these causes are much rarer than coeliac disease and are easily distinguished by the signs of chronic nephritis.

(3) *Other varieties of endocrine disorder.*—There are only two varieties of endocrine disease to consider in relation to diagnosis. The first is hypothyroidism, of which the congenital variety (cretinism) is easily distinguished by the history of delayed mental development with early epiphyseal retardation associated with adiposity and other signs of hypothyroidism. Juvenile myxoedema in the latter years of childhood shows stunted growth and may exhibit infantilism, but the typical adiposity, the dry skin with subdermal infiltration, the coarse features, and mental retardation serve easily to distinguish them. After puberty a considerable degree of hypothyroidism may arise in primary anterior lobe hypopituitarism and it is the cause of the epiphyseal retardation, but no real resemblance to juvenile myxoedema occurs, and in the patients that we have seen the diagnosis was not in doubt.

The cases to be described in Chapter 8, primary hypogonadism, which show sexual infantilism, are clearly distinguished by the absence of growth defect.

Treatment

Retarded growth and sexual infantilism both require attention. In the younger children the growth factor is of primary importance, and either anterior pituitary powder by the nose or if injections are practicable Antuitrin G (Parke Davis) is given, the latter in a dosage of at least 3–5 c.cm. twice weekly. Sometimes a whole gland preparation, usually Paines and Byrne's whole pituitary gland, dose gr. v–gr. xv, is given at the same time by injection, as a whole gland preparation is thought to accentuate the action of the growth hormone. Owing to the possibility of the development of an antibody to the growth hormone, treatment should be remitted every few months for a few weeks. In children this generally happens incidentally from one cause or another. Small doses of thyroid gland have been given to most of the cases but in the younger children there is no

obvious indication for it. In our later cases we have given thyroid gland to the tolerance of the patient.

In the cases seen for the first time in the adolescent years the sex factor assumes greater importance, and before starting treatment the relative defects of growth and sexual function must be considered. If the growth defect is the more prominent feature, energetic treatment on the lines indicated above should be carried out; later, gonadal stimulating treatment can be added if required. If, however, there is only a relatively slight growth defect with sexual infantilism, then no time should be lost in stimulating the sex development as described in Chapters 4 and 8. It is to be remembered that development of the sexual function will help closure of the epiphyses and thus prevent growth from taking place. Thyroid gland should be given and increased to maximum tolerance in the adolescent cases.

The table, p. 117, gives exact particulars of treatment. We now use larger doses than formerly and seldom prescribe less than 5 c.cm. of Antuitrin G twice weekly in a case of well-marked growth defect. The question of how long treatment should be carried out is a difficult one. An initial course of three-months injections is our usual routine and this is always followed by another. At the end of that time some cases will continue to grow and develop without further treatment, but the majority require it. In the younger patients after six-months treatment with pituitary powder we now omit treatment for several months to obviate any risk of precocious sexual development. The adolescent cases are treated until further growth and development cannot be obtained. Examination of the epiphyses for development is undertaken from time to time so that a growth-stimulating hormone is not given after ossification has occurred.

Prognosis and Results of Treatment

Without treatment the prognosis is poor. The patients remain stunted and thin, adiposity may supervene later in life. In some cases a degree of sexual development takes place; in a few patients this may approach normal and pregnancy may occur. As in most varieties of pituitary

disorder, premature senility is found and we have illustrated one such patient in Plate No. 25.

What is the prognosis if treatment is attempted? There are few more difficult questions to answer, but it may be said that the striking results that can be obtained experimentally in animals cannot as a rule be reproduced in the human being. This is not to say that treatment is of no avail for in our opinion treatment is valuable, but very spectacular results are not to be expected. We have quoted above at some length a case (No. 61) in which there can be no reasonable doubt that treatment caused growth, but there are very few instances so clear-cut. The only way to prove the matter is to collect a large number of results of careful treatment. In order to show clearly the evidence on which our conclusions are based, we have prepared a table giving treatment and results in the first fourteen consecutive cases which have been treated for not less than six months. On looking at this table it should be remembered that these children were sent to us for small size, under-weight, or under-development, that almost all gave a history of having grown slowly from birth, and that except in one case, No. 61, who was admitted to hospital, no change was made in environment. Furthermore, five of the patients were over $15\frac{1}{2}$ years old, not an ideal age to stimulate growth. When we look at the details we find that one case, No. 49, did not show any improvement at all and two, No. 66 and 73, showed very little change. In Case No. 60 secondary hypogonadism was more important than the relatively slight growth defect, and this was treated with excellent result. Of the remaining nine patients, all showed general improvement with the loss of such symptoms as nervousness and bilious attacks. A gain of height occurred in all, with an increase in weight, which in some cases was considerable. The increase in weight is significant because the difficulty of fattening the small thin child is well known, and no instructions were given regarding extra diet. It can be seen from the table that in several cases treatment appeared to initiate normal development, shown by measurements taken some time after treatment had ceased.

Case No.	Age, Sex	Duration of Treatment in Months	Treatment	Increase		Remarks
				Height in in.	Weight in lb.	
60	15, F.	24	P. 500 R.U. twice weekly; W.P. as well, 6 months; T.F. gr. $\frac{1}{2}$ B.D., 6 months	4	10	Periods appeared and became regular. Secondary sex characters developed. Appetite improved
61	16, F.	18	1 c.cm. A. daily, 9 months; 1 c.cm. A.G. daily, 9 months; P.R. 500,000 units weekly, 3 months P.A.	4	25.5	Secondary sex characters developed in part. Considerable general improvement
62	5, F.	13	P.A.	6	11	Measurements were taken 10 months after treatment had stopped
52 49	5, M. 10 $\frac{5}{13}$, M.	48 8	P.A.; T.F. gr. $\frac{1}{4}$ B.D., 8 months 1 c.cm. A.G. twice weekly, 5 months; 2 c.cm. A.G. twice weekly, 3 months 5 c.cm. A.G. twice weekly	8.75 nil	19 nil	Bilious attacks stopped. More energy Probably insufficient dosage
50	16, M.	24	1 c.cm. A.G., 3 times weekly A.G. 3 c.cm. twice weekly, 12 months; T.F. gr. i B.D., 2 months A.G. 1 c.cm. twice weekly	6	20	Improved immensely in build and also mentally in gain of confidence
51 73	16, M. 12 $\frac{1}{2}$, M.	10 12		2.25 1	5 3	Gained confidence. Muscles developed No results, except that he felt better
53	14, M.	6		not available		Doctor reports that after 3 months he started to grow and has developed well since, physically and mentally. At the end of 2 years, weight had gone up 30 lb. and height 5.5 in.
66 67	10, M. 16, M.	7 19	1 c.cm. A.G., every other day P.A., 11 months; 1 c.cm. A.G. twice weekly, 8 months	0.25 3.25	8 15	No result Seen 1 year after treatment had stopped he had grown a further 2.75 in. General condition much improved
87 99	15 $\frac{5}{12}$, M. 10, M.	9 12	A.G. 5 c.cm. twice weekly; T.F. gr. $\frac{1}{2}$ B.D. P.A.	3.75 2.25	15 11	Very much improved Remarkable improvement in intelligence; I.Q. raised from 65 to 80, also physical improvement
105	14, F.	24	W.P. gr. xv twice weekly, 7 months; A.G. 2 c.cm. twice weekly, 2 months; A.G. 1 c.cm. three times weekly, 3 months; P.W., 6 months; T.F. gr. i B.D., 24 months	1.75	10	Headache and bilious attack stopped at once. Considerable general improvement

A. Antuitrin
 W.P. whole pituitary injections
 T.F. fresh thyroid gland (B & W)
 P.W. whole pituitary powder
 P. Pregnyl
 A.G. Antutrin growth extract
 P.A. anterior pituitary powder
 R.U. Rat unit
 P.R. Progynon

These results are not proof that treatment stimulates growth in this syndrome, because the series is not sufficiently long, and the practical difficulties of observing patients over a number of years mean a long probation period before overwhelming evidence can be presented. But our opinion is, that the general condition of almost all the patients we have treated has been considerably and rapidly improved and that some effect on height has usually resulted. Another factor which may materially affect results in the future is more experience in dosage. Lawrence and Harrison (2) and Taylor (3) amongst many other writers have reported similar cases. Schaefer (4), who collaborated with Engelbach in his original study in 1932, has recently published a report of eighteen patients who have been treated for periods of from ten months to six years. His conclusions are of interest and we give his summary verbatim :

“Eighteen pituitary dwarfs with 4 exceptions, while treated with preparations of the pituitary growth factor, gained a greater increase in height than the normal increment for the time treated, while during periods of no treatment their gain was less than the normal increment. In those cases in which pituitary dwarfism and infantilism are associated a preparation containing other factors of the anterior lobe than the growth factor might be more efficacious.

“In early adolescence, sexual under-development is more important than moderate statural deficiency and should be given preference in treatment. The state of epiphyseal closure as an indication of how much longer growth will remain possible is a factor in the decision as to the indication for treatment with the growth hormone. The ultimate treatment of pituitary dwarfism has as yet not been attained. Further advances in the experimental field and better diagnostic ability will aid greatly.”

It will be seen how clearly these statements coincide with our views.

REFERENCES

- (1) Hastings Gilford, *The Disorders of Post-natal Growth and Development*.
- (2) Lawrence and Harrison, *Endocrinology*, 23 : 360, 1938.
- (3) Taylor, *ibid.*, 22 : 707, 1938.
- (4) Schaefer and Strichroot, *ibid.*, 26 : 599, 1940.

CHAPTER 6

HYPERPITUITARISM AND PUBERTAS PRAECOX

Hyperpituitarism

THIS condition is characterised by excessive growth and an early sexual development, both being due to hyperactivity of the anterior lobe of the pituitary. The weight at birth may be greater than normal but its significance is seldom recognised unless there is some other abnormality such as premature teeth. In the infantile and juvenile years comparison of the measurements with a standard table at intervals facilitates diagnosis. Genetic factors must be excluded as far as possible by enquiry into the family history. The epiphyses show normal or advanced development, and this, together with the absence of signs of hypothyroidism, will distinguish the cases from overweight due to cretinism.

In the later juvenile years we are all familiar with children who suddenly begin to develop very fast ; for example, a girl of 10 may grow 5-6 inches in a year, begin to menstruate and develop the form and secondary sexual characters of the adult woman, and the boy of 12 may develop in a corresponding way. As a rule, the excessive stimulus loses its force after a while and the individual settles down to normal development without showing any pathological symptoms, except that evidence of excessive pituitary stimulation may remain in the form of a disproportioned skeletal system with an abnormally long span and lower measurement. Even when this disproportion is the only pathological sign it is well to realise that the process is not a normal one, and this becomes quite obvious when we consider the more extreme forms of the syndrome. If the pituitary stimulus occurs very early in life, we have the

condition of *pubertas praecox*; when the growth stimulus does not die down, a condition of normal gigantism (as distinct from eunuchoid gigantism) results. Additional evidence is provided by the fact that, in hyperpituitarism also, a family history of endocrine abnormality is frequently found, and we shall emphasise resemblances to other pituitary syndromes. The chief importance of diagnosing the lesser degrees of hyperpituitarism lies in the fact that the unbalancing effect of the intense hormonal activity may produce abnormal mental symptoms, as in the following patient.

CASE No. 80.—Plate No. 26. This was a girl of 14 years who was referred to us for mental reasons. For some time her conduct had been abnormal, for she showed an intense and uncontrollable activity. At school, where she was incessantly in trouble, her influence was so bad that the question of her expulsion had been raised. At home she was beyond the control of her mother and she did not care for the company of boys or girls of her own age but sought that of a man of 21.

On examination, she was a bright vivacious girl with a high complexion who looked much older than her years, and was above the normal height of an adult woman. The measurements are of interest, and show the activity of the growth hormone in the

Case No. 80	Patient	Normal
Head . . .	21·5 in.	21·4 in.
Chest . . .	31·0 "	28·9 "
Abdomen . . .	27·0 "	24·5 "
Span . . .	71·0 "	59·0–63·5 in.
Height . . .	67·5 "	59·3–63·5 "
Lower Measurement .	37·0 "	29·6–32·3 "
Upper Measurement .	30·5 "	29·2–32·0 "

height and the length of the span, and by the abnormal difference of 6·5 in. between the upper and lower measurements. The pituitary sex hormone was normal, as shown by the well-marked development of the breasts and pubic and axillary hair and the fact that menstrual periods had been regular for a year. It can be seen from the plate that she was not fat but was well covered, and it is important to note the pelvic girdle of fat and the rather plethoric features. Radiography of the epiphyses showed them to be slightly advanced (2–3 years). The mother had a small thyroid adenoma.

CASE No. 74.—Plate No. 19. This was a girl of 11 years.

The maternal grandmother weighed 294 lb., the mother was stout, and a sister weighed 364 lb., having gained three stone after her last pregnancy. At the age of 6 years the patient started to grow rapidly, and during the last six months she had gained a lot of weight. Recently she had lost interest in her school-work and had appeared dull.

On examination, she was the maximum size of a girl of 16½ years and she showed adult sexual development. The measurements show the same characteristics as in the previous case.

Case No. 74	Patient, Age 11	Normal for Age of 11	Patient, Age 13½
Head	22·0 in.	20·9 in.	22·75 in.
Chest	35·0 "	26·0 "	38·0 "
Abdomen	34·5 "	22·4 "	34·0 "
Span	70·0 "	53·3-57·3 in.	70·0 "
Height	65·25 "	53·4-57·2 "	66·0 "
Lower Measurement	34·25 "	26·4-29·0 "	35·0 "
Upper Measurement	31·0 "	26·5-29·0 "	31·0 "
Weight	154·0 lb.	63·7-81·0 lb.	174·0 lb.

The thyroid gland was palpable. Menstruation had been regular for five months. Radiographic examination showed that the skull was normal and that the epiphyses were advanced in development by five years.

Since both the height and development of the epiphyses corresponded to the age of 16-17 years, it was clear that growth would soon stop, and the measurements two and a half years later confirmed this. During this time the development of the epiphyses advanced a further five years. At the age of 13½ years, despite the height, she did not look like a normal girl of 16-17 years because of the distribution of fat which resembled that seen in childhood pituitary obesity, indicating that there was an abnormality as well as an excess of pituitary secretion. The above cases will be commented on further (p. 122).

Engelbach (1) describes an interesting case of hyperpituitarism which developed into gigantism. The birth weight of the patient was 11 lb. Following a febrile attack at the age of 7 months, he began to grow rapidly, and at the age of 7 years his height was that of the average adult man. Puberty occurred between the ages of 9 and 10 years. At the age of 18 years he could support a man weighing 175 lb. on each outstretched arm. Until the age of 19 years he continued to grow larger and stronger and an extreme libido

developed. When examined at the age of 25 years the height was 92 in., the span 96 in., and the lower measurement was 8 in. longer than the upper. The epiphyses had closed, radiographs of the pituitary fossa were normal, and there was no evidence of pituitary tumour.

There are several points of interest in this case history. There was no family history of endocrine disease, but hypersecretion of the pituitary gland was evidently activated by an infection at 7 months. Notwithstanding the enormous growth, a fairly well-balanced skeleton resulted, indicating that a reasonable balance between the growth and sex hormones of the pituitary had been maintained, for the span was only 4 in. longer than the height, and while the difference of 8 in. between the upper and lower measurement was a large one, it was not very great in relation to the height. It is interesting to compare these figures with those of the case of eunuchoid gigantism reported on p. 169. There the span exceeds the height by no less than 10 in. and the lower measurement the upper by 15.25 in., although the height is only 74.75 in. A completely disproportioned skeleton had resulted from the fact that pituitary growth hormone had not been balanced by the production of gonadal secretion.

A family history of endocrine disease is often found, and Case No. 74, p. 120, is a good example. We have seen another family in which examples of hyperpituitarism, growth defect, and childhood pituitary obesity all occur. The activity of the growth and sex hormones is plainly shown by the above cases. The measurements indicate the influence of the former very clearly, for the span exceeds the height considerably and the lower measurement is greater than the upper measurement in patient No. 80 by no less than 6.5 in. The influence of the pituitary sex hormone in stimulating gonadal development is seen in the adult figure and appearance of both these children. This over-development is associated in both cases with some advance in development of the epiphyseal centres. This advance is usually found in patients with hyperpituitarism, and is due to the action of the gonadal secretions which have been stimulated by the pituitary gland. The patient No. 74 shows an advance in development of five

years, which corresponds roughly to the length of the bones, so that although the growth and sex hormones are excessive, yet they are fairly well balanced. The radiological age of the bones corresponds to their length, and as the sex hormones are obviously active, the rate of growth will slow down and the epiphyses join, thus preventing the development of a condition of gigantism. Patient No. 80 is not so well balanced, for the statural growth did not correspond to epiphyseal development when first seen; if the growth stimulus were to continue at the same rate, this case might well develop into gigantism. The stature of this patient is consequently much more out of proportion than that of the other child. As a matter of fact growth in this patient has since slowed down. In many of these children there is excess of weight relative to the height due to fat which accumulates in the same situations as it does in childhood pituitary obesity. Pelvic girdle fat is present in patient No. 80, while patient No. 74 does not look like a young adult at all, but rather resembles a middle-aged woman with abdominal and pelvic fat and fat on the thighs. It is interesting to note the high complexion and plethoric appearance of patient No. 80, for these features suggest a connection with childhood pituitary obesity, especially when it is remembered that the average height of the pituitary obesity cases is above normal. It seems likely that in hyperpituitarism there is an abnormality of pituitary secretion as well as an excess. By these statural and bodily characteristics minor degrees of the condition may be recognised, and this is important because of the frequency of mental symptoms in this group. In patient No. 80 it is quite clear that the hormonal activity excited the emotional centres and gave rise to an advanced emotional development. We have little doubt that the excessive activity and energy of this child was also produced by the general excitation of bodily processes due to excessive hormone stimulation. The same symptom occurs in hyperthyroidism where a middle-aged housewife with a toxic adenoma will work until exhaustion ensues because she feels that she cannot keep still. In the next section a case of *pubertas praecox* in a small boy will be described

who showed an even more uncontrollable activity, which we also ascribe to hormonal influence. The girl No. 80 was in danger of being expelled from school, but an explanation to the mistress and to the mother averted this and helped them to adopt better methods of control. Four years later she was at work in a laundry and was somewhat quieter. Such a condition of superabundant spirits and activity must often lead young people into exploits which infringe the law, and unless the underlying endocrine mechanism is recognised, serious results are likely to follow because the associations of prison life would be the worst possible treatment and might initiate a life of crime. On the Continent the condition is recognised by the provision of certain convents for taking girls who show precocious sexual tendencies and keeping them in quiet surroundings until the abnormal condition has passed off. In some cases this excessive activity does not occur and the child may be extremely nervous. For example, a boy, aged 13, was 7 in. above the maximum height for his age and his genital development was that of an adult. He suffered badly from attacks of migraine and nervousness.

Patient No. 74 (described above) shows another type of mental reaction. She was examined by the psychologist, who reported that her intelligence was normal for her age, but that if any task a little beyond her powers were set, she refused to make any effort at all. It seemed likely that owing to her appearance more was habitually asked of her than could be expected, and the child then refused to try and appeared dull in consequence. We have met other similar examples.

Diagnosis

Patients with hyperpituitarism resemble in measurements and build those cases of childhood pituitary obesity which show a marked excess of growth. They are distinguished by the absence of gross obesity and the presence of normal or advanced sexual development. See Plates No. 19, 26, 27.

Cases of primary non-adipose hypogonadism (*q.v.*) are also tall but are clearly recognisable by their thin sparse

build, retarded sexual development, and delayed ossification. The diagnosis might also be confirmed by finding excess of sex hormones in the urine of hyperpituitary patients. The possibility of the condition being due to tumour formation of the eosinophil cells of the anterior lobe of the pituitary must be remembered, particularly in cases of gigantism, and these cases show loss of sexual function with progression of the tumour. Persistent headache would arouse suspicion. Confirmation of the diagnosis should be sought by repeated examination of the visual fields to detect early bitemporal contraction, which may at first be limited to the colour field, and by radiographic examination to see the result of pressure effects upon the sella turcica. At a later stage the ocular nerves may be involved and pressure on the 3rd ventricle may cause hydrocephalus. Acromegaly is due to an eosinophil tumour of the pituitary gland in adults, but it will not be dealt with as it is outside the scope of this book.

Prognosis

In most patients the prognosis is good, for the condition is usually self-limiting, but it should be regarded as evidence of pituitary dysfunction and the patient carefully observed.

Treatment

The children should be given plenty of rest, quiet surroundings, and a minimum of excitement. There is no certain means of controlling an excessive endocrine secretion or preventing the residual skeletal dysfunction which is likely to occur, but if the condition is recognised, much may be done by sedative methods to help the mental symptoms. We have not employed irradiation of the pituitary gland, which would only be justifiable in extreme cases. There is no doubt that gonadal hormones inhibit secretion from the anterior lobe of the pituitary, and this is a possible method of treatment in severe cases which we have not yet tried. If a tumour were present, it could be treated by deep therapy, or the question of surgical operation considered.

Pubertas Praecox (Macrogenitosomia Praecox)

This is a rare condition characterised by pre-adolescent hyperfunction of the genital system and accompanied by over-growth of all the tissues of the body with advanced osseous development, thus only differing in degree from hyperpituitarism. Pubertas praecox has been described in relation to a variety of endocrine conditions and we have made a thorough study of two cases, the first of which showed most remarkable mental symptoms, and at autopsy a tumour of the floor of the 3rd ventricle was found; the second has been under observation for seven years without any pathological entity showing itself, and the condition is now merging into normal development. We think that this patient forms a link connecting pubertas praecox with the case of hyperpituitarism just described, and after discussion of the various factors a hypothesis linking all the causes of pubertas praecox will be formulated.

CASE No. 131.—Plates No. 28 and 28A. This case has been fully reported by one of us (H. S. Le M.) (1) in collaboration with Dorothy Russell, who carried out the pathological investigations. The patient was the first child of healthy country folk in whose history no endocrine disease could be found. He was born June 24, 1929, and weight at birth was $7\frac{1}{2}$ lb. He cut his teeth without trouble and walked at 14 months, and at about that time pubic hair appeared and the genital organs began to develop very fast. The weight chart shows a rapid increase from that point and his strength developed at a similar rate. At the age of 1 year and 10 months sexual symptoms of a very unusual kind were noticed. He would crawl across the floor to a woman seated in a chair, put his arms around her legs, suck his thumb and his penis would become erect. He showed a preference for particular women, who in the end could not be invited to the house. He was only attracted to adult women up to 40 years of age, and until a year later he took no interest in little girls. With the development of sexual impulse, weight, height, and strength, a ceaseless activity became apparent which rendered him more and more difficult to control, for he never became tired and knew no fear. He came under observation at the age of 2 years and 7 months in January 1932.

Physical examination.—He had the weight of a boy of 8

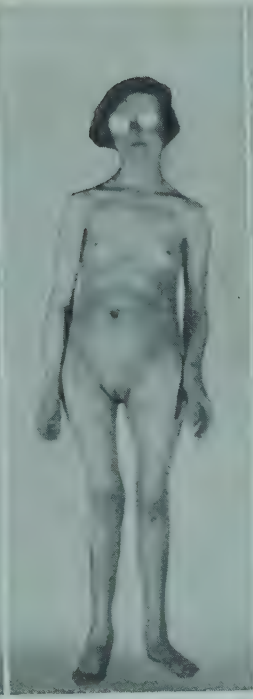
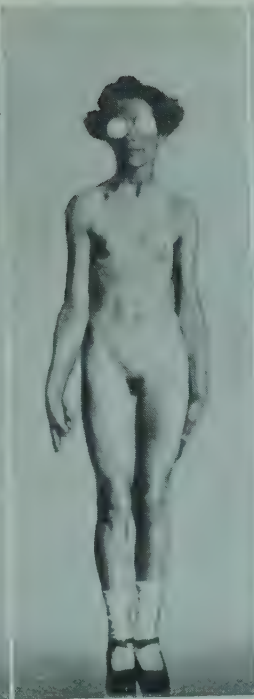
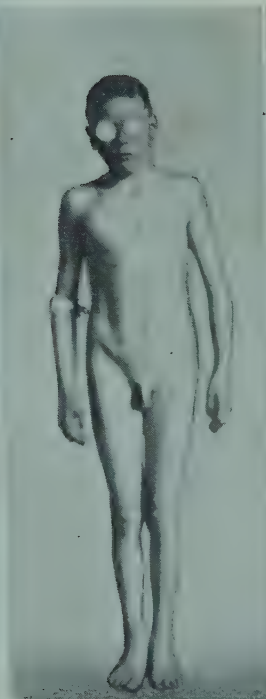


PLATE 22. CASE 140.

Age 15½ yr.; Wt. 77 lb.; Ht. 56½ in. Growth defect: poor muscular development: no pubic hair

PLATE 23. CASE 98.

Age 13½ yr.; Wt. 73 lb.; Ht. 58 in. Note ageing of the face.

PLATE 24. CASE A6.

Age 21 yr.; Wt. 84 lb.; Ht. 55½ in. Growth and sex defects following steatorrhoea.

PLATE 25. CASE A7.

Age 38 yr.; Ht. 57½ in. Shows puny development, sex defects and ageing.

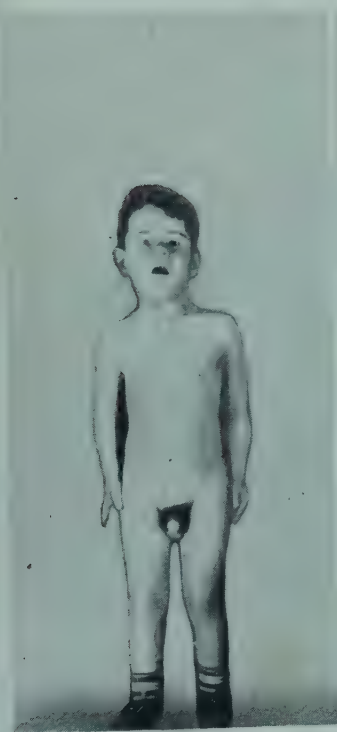


PLATE 28. CASE 131.

Age 2 yr. 8 mth.; Wt. 48 lb.; Ht. 41½ in.



PLATE 28A. CASE 131.

Age 3 yr. 11 mth.; Wt. 72 lb.; Ht. 49½ in.



PLATE 26. CASE 80.

Age 14 yr.; Wt. 152 lb.; Ht. 67½ in.



PLATE 27. CASE 143. Age 12 yr. 9 mth.; Wt. 112 lb.; Ht. 66 in. Epiphyses advanced. Adult sexual development.
 PLATE 29. CASE 132. Age 8 yr.; Wt. 100 lb.; Ht. 61 in. Corresponds to a boy of 12½ in height. Note advanced sexual development.
 PLATE 30. CASE 132. Age 14 yr.; Wt. 143 lb.; Ht. 65 in. Shows mature muscular build and ageing.
 PLATE 31. CASE 82. Age 12 yr.; Wt. 98 lb.; Ht. 60½ in. Shows precocious development after treatment. Cf. broad hands with Plate No. 38.



PLATE 33. CASE 128. Age 23 yr. Wt. 210 lb.; Ht. 63 in. Note hirsutism, arms, legs, face and well-marked eyebrows.
 PLATE 34. CASE 129. Age 14½ yr.; Ht. 64 in. Moustache present, pubic hair of masculine type, marked eyebrows. Mature appearance. Cf. with hyperpituitary types.
 PLATE 35. CASE 127. Age 23 yr. Wt. 210 lb.; Ht. 66 in. Mature appearance. Trunk obesity. Masculine distribution of pubic hair.



PLATE 37. CASE 54.
Age 16½ yr.; Wt. 101 lb.;
Ht. 65 in. Lower
measurement exceeds
upper by 5 in. Typical
thin build.

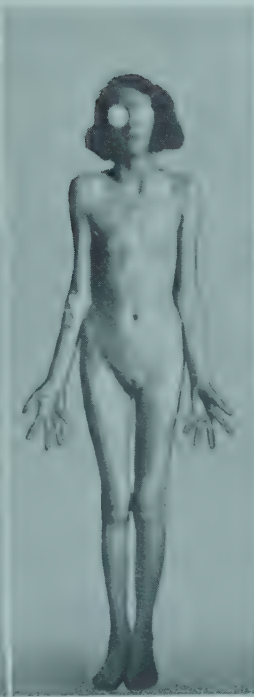


PLATE 38. CASE 138.
Age 15½ yr.; Wt. 95 lb.;
Ht. 65½ in. Epiphyses
retarded; menstruation
absent; uterus small. Cf.
long hands with Plates
30 and 31.



PLATE 39. CASE A1.
Age 42 yr.; Wt. 79 lb.;
Ht. 66½ in. Lower
measurement exceeds
upper by 4 in. Note
absence sexual develop-
ment.

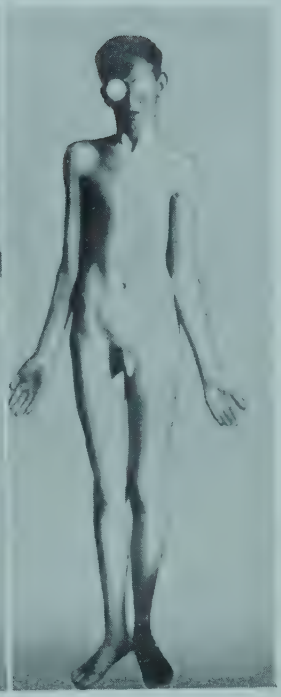


PLATE 40. CASE 56.
Age 13½ yr.; Wt. 92 lb.;
Ht. 66½ in. Lower
measurement exceeds
upper by 7½ in.

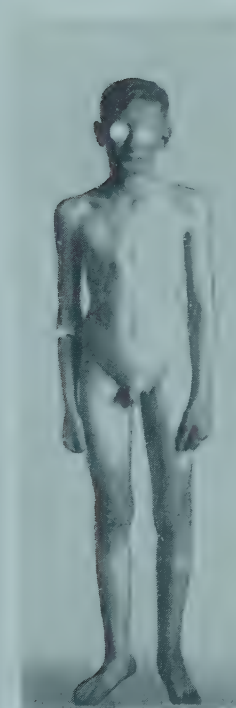


PLATE 41. CASE 69.
Age 13½ yr.; Ht. 61 in.
Lower measurement 4 in.
longer than upper; epi-
physes retarded. Condi-
tion still infantile at
15½ yr.



PLATE 42. CASE A2.
Age 27 yr.; Wt. 180 lb.;
Ht. 68½ in. Lower mea-
surement 5 in. longer
than upper. Note femi-
nine contour and dis-
tribution of pubic hair.



PLATE 43. CASE A4.
Age 23 yr.; Wt. 168 lb.;
Ht. 69½ in. Note puny
genital development.

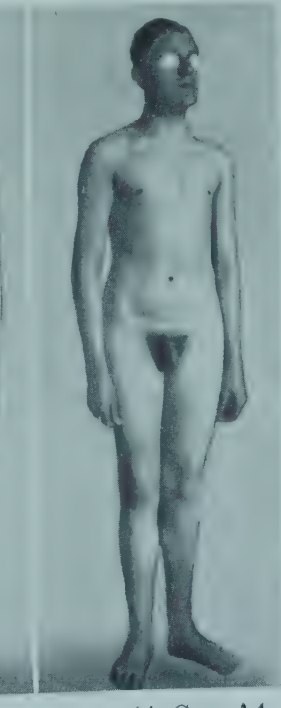


PLATE 44. CASE A4.
Shows genital enlarge-
ment after treatment.



PLATE 47. CASE 146.

Age 1 yr.; Wt. 15 lb.;
Ht. 22½ in. Physically
and mentally retarded.
Epiphyses delayed.

PLATE 46. CASE 144.

Age 4 yr. 2 mth.; Wt.
38 lb.; Ht. 39 in.
Shows effects of treat-
ment.

PLATE 48. CASE 147.

Age 10½ yr.; Wt. 91 lb.;
Ht. 54 in. Emaciation
above and obesity be-
low umbilicus. Ageing
of face.

PLATE 45. CASE 144.

Age 1 yr. 9 mth.; Ht. 29½
in. Epiphyses retarded.

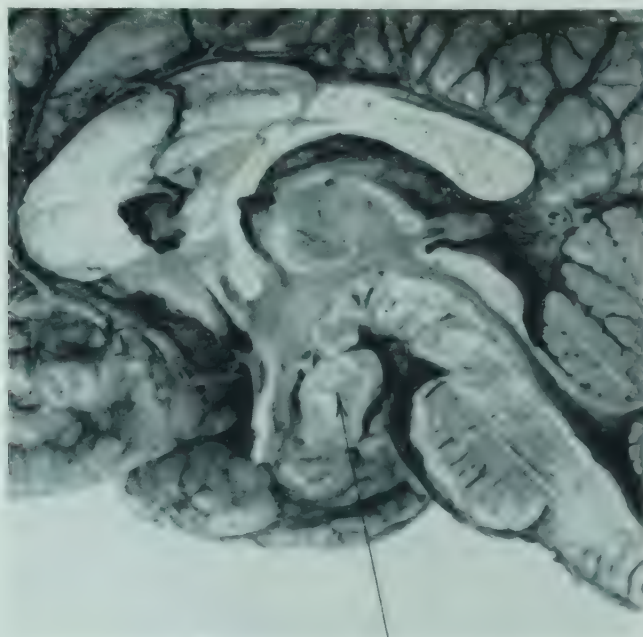


PLATE 49. CASE 131.

Sagittal section of brain.

(49 lb.) and the height of a boy of $4\frac{1}{2}$ ($41\frac{1}{2}$ in.) and was remarkably muscular. Overlying the muscles was a layer of fat. The hair of the head was copper red, coarse and abundant, the eyebrows well marked, the eyes hazel brown. The child had rather a wild half-excited expression, the outward sign of the almost maniacal activity which possessed him. The teeth were perfect and a complete set were present, and the development at this stage was normal; later it became slightly advanced. The hands were broad and strong and the breasts were undeveloped. Pubic hair was present with a horizontal upper margin. The penis and testes were developed to more than half adult size. The legs were very muscular and hair was present on the outer aspects and on the back. No abnormality could be found in the abdomen, the central nervous system, or chest. The blood-pressure was 90/60. Some mixed astigmatism was present and he had a habit of screwing up his eyes.

Mental characteristics.—The most striking feature was the exaggerated restlessness. He seized upon object after object without giving his attention to anything for more than a moment. If restrained he became bad-tempered. Only under general anaesthesia could a blood-pressure reading be obtained. On the cognitive side he was normal for his age, he understood all that was said to him, could recite nursery rhymes, and his memory was excellent. The voice was gruff, and articulation was not distinct and never became quite clear. He showed affection for his father and mother and never made sexual advances to her.

Investigations.—Stereo radiographs of the skull showed no abnormality except large size. Radiography of the epiphyses showed advanced development on the average to about the age of 10. Examination of the urine was normal as was the blood count. The sigma reaction of the blood serum was negative.

Subsequent history.—As the patient appeared to correspond in every way to the cases of virilism and pubertas praecox reported in connection with adrenal tumour, the abdomen was explored by Mr. Joyce on February 22, 1932. The right kidney was felt to be larger than the left. No adrenal tumour was found but the mesentery contained a number of enlarged glands, some of which were removed, and a histological report obtained from Dr. Mills was as follows: "The nodule from the mesentery is a hyperplastic lymph gland the sinuses of which are packed with lymphoid cells". We felt certain that there was no tumour of any size in connection with the right kidney; the left kidney was not so accessible, so we determined to explore the left kidney from behind. The left suprarenal gland was exposed by Mr. Joyce on

May 5, 1932, and it appeared normal. He was discharged from hospital in August 1932 when he was 3 years and 2 months old. He had grown to the height of a boy of 6 and the weight of a boy of 7. The strength and activity remained exceptional, and at the end of 1932, at the age of $3\frac{1}{2}$ years, he pushed his father's motor bicycle and side-car out of the shed and on to the lawn in the dark.

In April 1933 sexual impulses became stronger than ever, and led to repetition of the efforts to get at a woman's legs as described above. This determined us to undertake further exploration, and he was readmitted to hospital in May 1933, aged 3 years 11 months. The abdomen was explored again by Mr. Joyce in the hope that the enlarged glands might have disappeared and that an aberrant adrenal tumour might be found. The enlarged glands were still present and no adrenal tumour could be found. The right testis was then removed and a few weeks later the right suprarenal gland was removed also. Shock was combated after this operation with Coramine and Eucortone and Adrenalin. Within six days he was trying to get out of bed, and within eight days sexual symptoms had reappeared. Following removal of the testis and adrenal he became somewhat more docile, but was still very far from normal. The sexual urge was reduced as he would only make advances to women if they played with him on the floor. His temper improved but he never showed the least appreciation of right and wrong. When he was 4 years and 5 months his strength was such that he could wheel a barrow containing $1\frac{1}{2}$ cwt. In February 1934 he developed rheumatic fever and died of endocarditis in April, aged 4 years 10 months.

Anthropometry.—The weight and height charts, p. 131, are of great interest. The former is available for the whole of his life. When the genital organs started to grow at 14 months the weight curve crossed the optimal curve and started a rapid ascent to reach the weight of a boy of 12 years just before death. The height curve is also phenomenal. During the first seventeen months under observation he grew $8\frac{1}{4}$ in., then the testis and adrenal were removed and he failed to grow for a short time: during the rest of his life, ten months, he grew $3\frac{3}{4}$ in., almost attaining the height of a boy of $10\frac{1}{2}$ years. During the first year that he was under observation growth was faster in the lower measurement than in the upper measurement. During the last year of his life growth practically stopped in the long bones, while rapid growth proceeded in the flat bones, as shown by the increase in length of the upper measurement. The explanation is afforded by the epiphyseal development, which was already bringing about a stoppage of growth. If he had lived he would have been a

dwarf with a long upper measurement and short legs. These facts are clearly shown in the following table :

Age in Months	Height in Inches	Upper Measurement	Lower Measurement	Epiphyseal Development (Average) in Years
32	41½	22½	19	10
46	48	25	23	13
58	53½	29½	24	15

The post-mortem findings are of sufficient interest to report in full.

Summary of necropsy.—Heart failure. Acute rheumatic endocarditis and myocarditis. Macrogenitosomia praecox (pubertas praecox). Old operations : excision of right suprarenal body and right testis.

Focal organising and organised rheumatic pericarditis. Rheumatic endocarditis involving mitral, aortic, and, to less extent, tricuspid valves. Fatty degeneration of myocardium. Very slight atheroma of aorta. Acute and chronic back-pressure congestion with areas of haemorrhagico-purulent broncho-pneumonia in lungs. Congestion and conspicuous back-pressure atrophy of centres of liver lobules. Moderate fatty degeneration of liver. Congestion and focal post-mortem digestion of pancreas. Congestion, severe albuminous and slight fatty degeneration of kidneys. Congestion and subacute inflammation (microscopic) of spleen. Subacute inflammation (microscopic) of coeliac gland and of mesenteric gland. Scanty lipoid, mostly in miliary nodules, and dark-brown pigment zone in left suprarenal body. Prostate 3 cm. from side to side \times 1.5 cm. from before back. Distension of seminal vesicles (left $4.5 \times 2 \times 0.7$ cm.; right $3.7 \times 1.5 \times 0.7$ cm.) with glairy grey contents. Vasa deferentia 0.25 cm. diam., becoming thicker (0.4 cm. diam.) near seminal vesicles. Left testis $3.5 \times 2 \times 2$ cm. Epididymis 4 cm. long; globus major 0.8 cm. diam. with sessile miliary hydatid of Morgagni on surface. No macroscopic abnormality in thyroid gland nor in completely glandular thymus.

Weights.—Heart, 248 g.; thyroid gland, 6 g.; thymus, 23.1 g.; left suprarenal body, 4.2 g.; spleen, 160 g. (part missing); liver, 893 g.; pancreas, 32 g.; kidneys, 213 g.; parathyroid glands, 0.059 g. together; pituitary body, 0.475 g.

Brain.—The interpeduncular space is occupied by a firm, smooth, opaque creamy-white mass (1.35 cm. from side to side \times 0.8 cm. from before back \times 1.5 cm. from above down) which is firmly attached to the right corpus mamillare and to the

tuber cinereum at a point slightly to the left of the midline (Plate No. 49). The cut surface of the mass is smooth and is composed of glistening greyish-white tissue traversed by a few linear white streaks. The corpora mammillaria are symmetrical and of full size (0.5 cm. diam.). There is slight pocketing of the floor of the 3rd ventricle where the mass is attached to it. Further, the cavity of the 3rd ventricle extends down to the cut end of the pituitary stalk, which is widely patent. The pineal gland and the rest of the brain appear normal. There is no internal hydrocephalus.

The *pituitary body* measures 1.7 cm. from side to side \times 0.8 cm. from before back \times 0.6 cm. from above downwards. It appears normal both superficially and on horizontal section.

Microscopic examination.—The mass occupying the interpeduncular space is composed of tissue closely resembling that of the brain proper. Both in the central parts and at the periphery are conspicuous nuclear collections of fully differentiated neurons. The bodies of the neurons vary greatly in size and shape, some being rounded and apparently unipolar and others multipolar. The latter are usually larger than the former. The cytoplasm of both types contains well-defined Nissl bodies. Between these collections of neurons are a few conspicuous bundles of myelinated nerve fibres. The junction of the tumour with the right mammillary body is traversed by some of these bundles. Numerous isolated myelinated fibres are also present in the tissue between the neurons in other parts of the tumour. Specific methods for demonstrating neuroglia reveal all the normal elements in the supporting tissue. There is a slight excess of fibrillary astrocytes at the periphery, and amongst these cells are a few astroblasts. Microglial and oligodendroglial cells are also distributed in approximately normal proportions. The oligodendroglial cells sometimes lie in short rows along the myelinated fibres and constitute a so-called interfascicular glia.

Serial microscopic sections of the *hypothalamus* reveal no abnormality: the supraoptic, paraventricular, tuberal, infundibulo-mammillary, and mammillary nuclei are all of ordinary size and free from appreciable degeneration. There is no meningitis nor encephalitis. The *pineal body* is normal except for two microscopic cysts containing a little hyaline eosinophil material and lined with neuroglial fibres. The *pituitary body*, examined by serial section, appears normal. The *left suprarenal body* appears normal. Dr. H. W. C. Vines has kindly examined sections by the ponceau-fuchsin method, and reports that "the result is an almost entirely negative reaction. A few red spots are present in some cells, but I should not be prepared to say that these were

outside the limits of normal." The *pancreas*, *thyroid* and *parathyroid glands* and *thymus* appear normal. The *right testis* contains conspicuous groups of interstitial cells. Numerous karyokinetic figures are present in the cells in the tubuli contorti, and in many places the lumina contain spermatids and groups of spermatozoa.

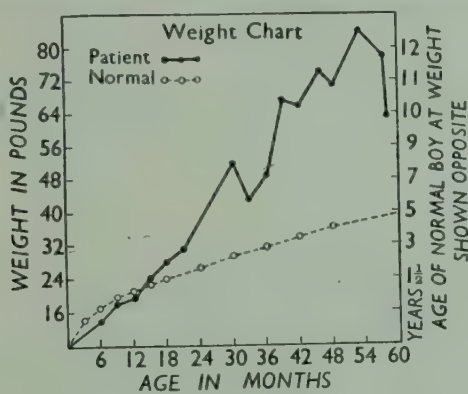


FIG. 4

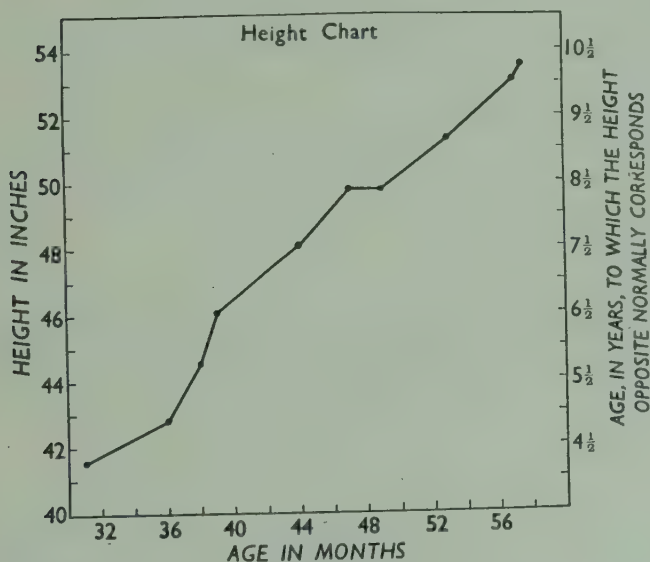


FIG. 5

CASE No. 132.—Plates No. 29 and 30. This case has not been previously reported. This boy was born July 4, 1927, of normal parents, the confinement being uneventful. He weighed $9\frac{1}{4}$ lb. and the mother states that he was tall and that the genital organs were large. The father's family are all tall, one of his sisters being about 6 ft. high. When he attended hospital, exactly 5 years old, the mother complained that he was "nervy", restless at night, quarrelsome with other children, and more than

usually mischievous, so that he could not be trusted alone with his little sister, aged $2\frac{1}{2}$ years. He masturbated, erections occurred, and he suffered from enuresis. He went to school where he got on fairly well but he had great difficulty in sitting still.

On examination, he had the height (50 in.) and weight (63 lb.) of a boy about 8 years old. He was exceptionally strong

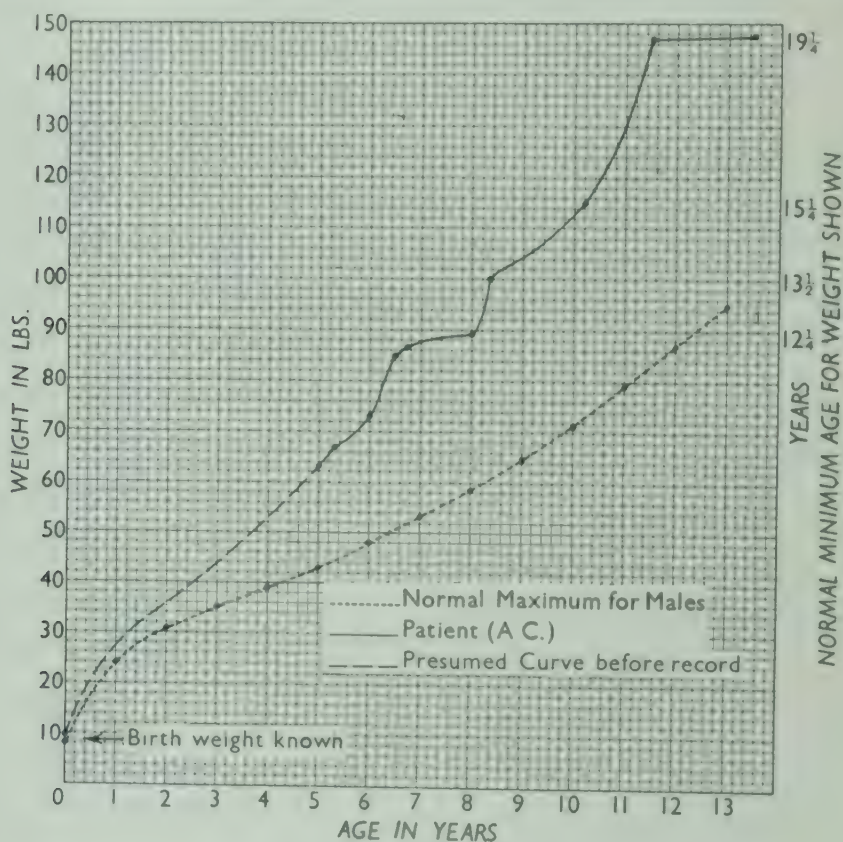


FIG. 6

and muscular and did not show the covering of fat over the muscles which was present in the first case. The genital organs were abnormal, the penis being almost adult size, the scrotum well developed but the testes were relatively small. Pubic hair was appearing but there was none in the axillae. The hair of the head had a reddish tinge and the eyebrows were very well marked. No evidence of adrenal tumour or other pathological condition could be found. A stereo-radiograph of the skull showed no abnormality and the epiphyseal development corresponded to the age of 12 years. The Wassermann reaction of the blood serum was negative.

Subsequent history.—The following table shows the measurements that have been taken during the eight years that he has been under observation. From these measurements a height and weight chart have been constructed.

Case No. 132	Age					
	5 Years	7 $\frac{1}{2}$ Years	8 $\frac{3}{4}$ Years	10 $\frac{1}{2}$ Years	11 $\frac{1}{2}$ Years	13 $\frac{1}{2}$ Years
Head .	..	20.5 in.	21.0 in.	21.0 in.	21.0 in.	21.5 in.
Chest .	..	29.5 "	30.5 "	32.0 "	34.0 "	34.0 "
Abdomen	..	27.5 "	27.0 "	28.0 "	31.0 "	31.0 "
Span .	..	61.0 "	64.0 "	66.0 "	70.0 "	70.0 "
Height .	50 in.	59.0 "	61.0 "	63.5 "	64.5 "	65.0 "
Lower M.	..	29.5 "	32.0 "	32.0 "	32.5 "	33.0 "
Upper M.	..	29.5 "	29.0 "	31.5 "	32.0 "	32.0 "
Weight .	63 lb.	86.0 lb.	100.0 lb.	115.0 lb.	147.0 lb.	147.0 lb.

From the graph Fig. 7 it can be seen that growth during the first four years is very rapid, reaching the height of a boy of

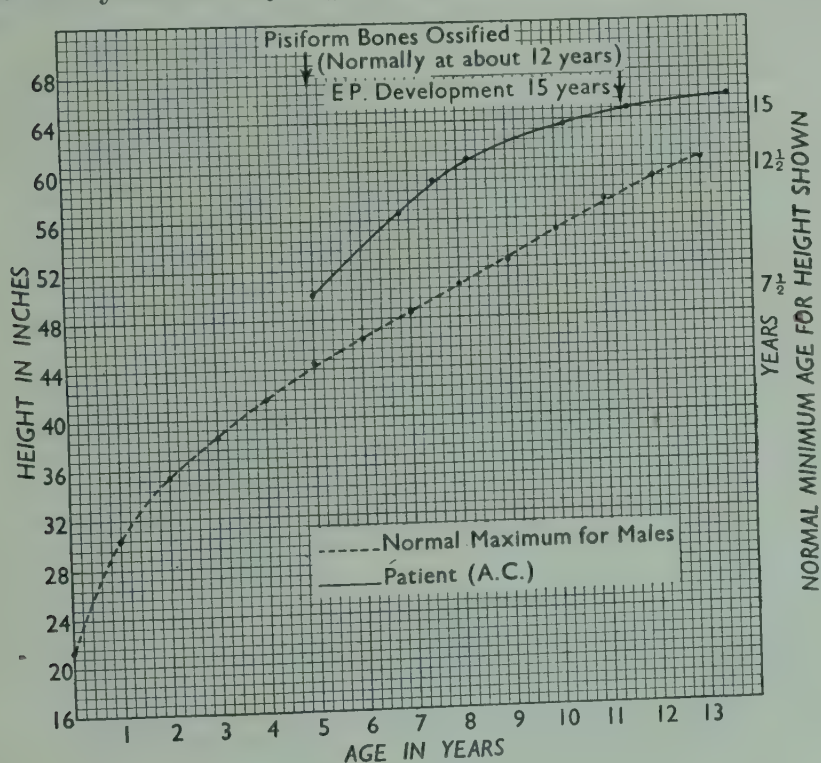


FIG. 7

12 $\frac{1}{2}$ years by the age of 8, then growth becomes slower and practically ceases by the age of 11 $\frac{1}{2}$ years when he attains the

height of a boy of 15. The weight (Fig. 6) shows no indication of slowing down at $11\frac{1}{2}$ years but nevertheless the rise ceases abruptly at that point, and two years later he remains the same weight. This excess weight is not due to fat but, as can be seen from the plates, is due to muscular development and a more mature build than would be normal for his height. When he first came under observation the epiphyseal development was seven years advanced; at $11\frac{1}{2}$ years it is about three and a half years advanced; at $13\frac{1}{2}$ years it is advanced by about five years. It will be seen from the table of measurements that practically no growth has taken place in the lower measurement during the last five years while the upper measurement has grown 3 in. It is evident that the growth stimulus became weaker at the age of 8 years and that epiphyseal development also began to exert an influence in stopping growth, so that the flat bones, as represented by the upper measurements, grew relatively fast. But a partial contradiction is shown in the fact that the long bones of the arms continued to grow at a rapid rate until the age of $11\frac{1}{2}$ years, reaching a length corresponding to the age of 17 years. Growth at no time reached the extraordinary rate recorded in the previous patient and the epiphyseal development has also retained a more normal relation to his stature; for example, at the age of 5 years he was the height of a boy of $7\frac{1}{2}$ years and the epiphyseal development corresponded to 12 years; at the age of $11\frac{1}{2}$ years both the height and the epiphyseal development correspond to the age of 15 years; at the age of $13\frac{1}{2}$ the height was almost unchanged while the epiphyseal development corresponded to 19 years. Therefore the upper and lower measurements have maintained a reasonable relation to one another. From the direction of the height and weight curves and from the state of development of the epiphyses it is obvious that very little further growth is to be expected, so that in a few years time this boy will be practically normal in stature and development.

There are other points of interest arising during the long period of observation. The propensity for mischief of which complaint was first made, persisted for several years. When he was $7\frac{1}{2}$ years old he attempted to assault a little girl, but this is the only trouble relating to his advanced sexual development that has been recorded. When aged $8\frac{1}{2}$ years he was examined by the psychologist, who reported that his intellectual development was above the average for his age (I.Q. 100 on Stanford-Binet scale), but that his attainments were low. If his real age were forgotten he appeared imbecile, and probably at school he was given tasks beyond his ability and discouraged in consequence. There were no signs of emotional or instinctive pre-

cocity. He played with boys of his own age regardless of size and his mental outlook was the same as theirs. Since then his general behaviour has improved, the restlessness and mischievousness have lessened, and a recent report from his schoolmaster states that his work and conduct are improving and he is gaining more control over himself. At the age of $10\frac{1}{2}$ years enuresis ceased. The penis was very large from an early age, but it was not until about $11\frac{1}{2}$ years that the testes also reached adult size. Emissions have not yet occurred. Pubic hair is very well developed and hair is present in the axillae and on the upper lip, but shaving is not necessary. The general development is very muscular, but there has been little change in this respect during the last two years. A radiograph of the skull shows hyperostosis in the occipital region but nothing else abnormal.

General Symptomatology

It is interesting to note in these two patients the points of resemblance to the cases described under the heading of hyperpituitarism. Patient No. 131 shows in a very exaggerated form the energy, uncontrollable activity, and sexual proclivities of patient No. 80, p. 120. Patient No. 132, p. 131, affords another close link with the hyperpituitary group because his condition is now merging into normal development and is almost certainly due to endocrine imbalance rather than to a gross lesion such as a tumour. Other examples of this type are afforded by a family reported by Rush (32) in which all male members, the father and two sons, developed precociously. In the case of the father, who was 33 years old when examined, sex development had been complete at about 5 years of age and he was attracted to the opposite sex at the age of 8. Growth was fast and he was larger than his playmates until the age of 14 years, when he stopped growing so that his adult stature was somewhat below the average. The two sons, aged 5 and 8, showed characteristic pictures of pubertas praecox and there were no less than five other similar instances in four generations of the family. The condition seems therefore to have been genetically determined and Rush suggests that an abnormal response to gonadotropic hormones may have been inherited. Pubertas praecox, like a number of other endocrine conditions, was first described in relation to a tumour formation and then

found to occur where functional imbalance alone existed. The cardinal symptoms of this condition, the somatic and genital overgrowth, and advanced epiphyseal development and the mental abnormality, are all well illustrated by our patients. The strength of patient No. 131 was such that he could be placed in what has been called the "infant Hercules" class as distinct from the "obese type", which is well illustrated in a paper by Fordyce and Evans (21). This boy resembled our boy No. 131 in having red hair, and this has been noted in other cases. An abnormal hair growth is present in most of the male cases developing concurrently with a change in the voice. Enuresis is a very common symptom and was present in both our patients. Masturbation is usual, but emissions did not occur in the boy who died and have not yet occurred in the other patient.

Pubertas praecox is not limited to boys, for it occurs in girls associated with cortical adrenal tumour and tumour of the ovary but not with pineal tumours. The "infant Hercules" type does not occur in girls. A typical case described by Bennett (33) was a girl who first showed a bloody vaginal discharge at the age of 4 months and twenty-eight days later she had a menstrual discharge lasting two days. Since then she has had regular menstrual periods at twenty-eight-day intervals, with a haemorrhagic phase lasting three or four days. She grew rapidly and at the age of 4 years was the size of a girl of 6 years old, with the hip and breast development of a well-developed 14-year child. The breasts showed considerable development at the end of the first year, and from then enlarged and became tender the week before menstruation. The osseous development was advanced from three to seven years. Assay of the blood showed the presence of oestrin in the amount usually found in normal adult women one week before menstruation. Mentally she was classed as dull normal. She was very attracted to men. At the time when the case was reported it was thought that an ovarian cyst could be felt. The female patients also show enlarged external and internal genital organs.

The importance of the mental symptoms in this syndrome has already been stressed. The endocrine imbalance with

the exaggerated sexual impulse may produce abnormal sexual conduct or merely show itself in an exaggerated activity and propensity for mischief or an extreme shyness and nervousness may result. In the literature most of these cases have been classed as mentally dull, but care has to be taken in estimating the intelligence if error is to be avoided as has been emphasised already. The intelligence does not mature in proportion to the bodily structure and it is difficult not to expect an intelligence that corresponds to the size of the patient. In our most abnormal child (No. 131) the intelligence was above the average for his age; in the other patient (No. 132) it is slightly advanced, but this boy plays with companions of his own age rather than with those of his own size. It was very striking to see him walking hand in hand with his mother when he was 8 years old, showing the natural mental attitude of a child of that age, when he looked much too old to act in that way.

Diagnosis

The diagnosis is not difficult because the genital and somatic overgrowth make a distinctive picture. But considerable difficulty may arise, as in patient No. 131, in determining the underlying cause. Pubertas praecox has been found in association with the following conditions :

- (1) Pineal tumours.
- (2) Midbrain and hypothalamic tumours.
- (3) Inflammation of the midbrain.
- (4) Adrenal cortical tumours.
- (5) Gonadal tumours.
- (6) Physiological pubertas praecox.

Of these groups the midbrain and hypothalamic tumours are so rare as to be mainly of theoretical interest, and considerable difficulty in diagnosis is likely to be found as in our case which fell into this group. In the third group diagnosis may be helped by the history or signs of the underlying infection, *e.g.* encephalitis lethargia. Tumours of the ovary or testis may be seen or felt and form another extremely rare group associated with this syndrome.

Among tumours associated with pubertas praecox those situated in the pineal are found more frequently than any of the other types, but only in the male sex. Apart from the constitutional manifestations, the first signs may be recurrent mid-frontal headache and drowsiness which may be intermittent owing to an abrupt increase of pressure caused by the valve-like action of the tumour in the relatively narrow 3rd ventricle. Paralysis of upward movement of the eyes, and Argyll Robertson pupils occur. If calcification of the pineal is present, radiographic examination may show a lateral deviation or ventriculography may be of assistance.

The presence of an adrenal cortical tumour may be suspected if a lump is found in either hypochondrium or if an abnormal renal shadow is obtained by radiographic examination after intravenous pyelography or after injection of air into the peritoneum. Surgical exploration will be required to confirm the diagnosis.

Under the heading of physiological pubertas praecox we have classed those patients who exhibit this syndrome without obvious pathological lesion and who eventually pass into normal development. They form a link with the cases of hyperpituitarism described in the previous section. Our patient No. 132 is characteristic, as are the three patients of one family described by Rush (p. 135). The possibility of a patient being in this group should always be borne in mind. In the future hormonal urine assays on all these cases will be made and may be of value.

Treatment

Where no gross lesion can be found the treatment to be adopted is that suggested under hyperpituitarism. If the condition is so abnormal that something must be attempted, irradiation of one adrenal gland and the pituitary gland or both may be attempted. The removal of one adrenal and one testis appeared to have some effect in our first patient, but he did not live long enough to make that certain; in view of the post-mortem findings it is extremely unlikely that he would have materially benefited.

The successful removal of a cortical tumour in a male

case of pubertas praecox was first carried out by Lissner (3) (23) in 1931 (see p. 142). This boy was alive and well eight years after operation and the sexual symptoms had lessened. Until a preparation of adrenal cortical extract was available death from shock following removal of cortical tumours was the rule. The patient of Fordyce and Evans died twelve hours after such an operation. He was found to have metastases in the liver and brain. The authors also report a case of pubertas praecox in a girl of 2 years in which an adrenal cortical tumour was successfully removed with a relief of symptoms and subsequent normal development.

Pineal tumours have now been removed in a number of patients and surgery will have to be considered in future. Neale (37) reports a recent case in which deep therapy treatment to a pineal tumour following decompression benefited the neurological symptoms but did not affect the constitutional changes.

Gonadal tumours should be removed. Mannheimer (38) reports a case due to a right-sided granulosa cell tumour of the ovary in a 4-year-old girl. The tumour was removed and contained oestrin. The patient became more childish, sexual characteristics regressed, and menstruation ceased.

Discussion

It is of considerable theoretical interest to note the variety of causes which may underlie the clinical entity pubertas praecox. These have been listed above. Each group gives rise to a symptom complex clearly resembling our patients, and therefore it is suggested that a relationship exists between these varied causes. To construct a hypothesis to account for such a relationship each variety must be considered briefly.

Pineal tumours.—Only a small proportion of pineal tumours in children are associated with pubertas praecox. These cases are rare and always occur in boys. The embryonal tumours of the pineal, the teratoma, are usually associated with this syndrome.

In a recent review Bochner and Scarff (34) give exact particulars of all the verified cases of teratoma in the litera-

ture. There are nineteen in all and they constitute approximately 10 per cent of all reported tumours of the pineal. Of these nineteen cases, pubertas praecox is present in nine only. Of these nine cases many show signs of local and general compression of brain structures and the 3rd ventricle is generally involved. In the far more numerous simple and mixed tumours of the pineal body pubertas praecox has only been noted ten times. Full references are given in the above article.

The hypothesis that pubertas praecox is caused by a secretion from the type of pineal tumour usually present, a teratoma, is discounted by the fact that the syndrome occurs with other types of tumours. Another suggestion is that the destruction of the pineal removes an inhibitory effect on development. Askanazy and Brock (8) report the case of a girl with pubertas praecox and hypoplasia of the pineal; on the other hand Krabbé (7) notes a case of absolute destruction of the pineal without pubertas praecox; Klaproth (9) describes a boy of 15 with a pineal teratoma and infantile sexual development, and Zandren (30) furnishes a case of infantilism in which no trace of the pineal can be found.

It has been noted above that many pineal tumours press on contiguous structures and cause internal hydrocephalus, so that an influence upon the midbrain centres either directly or through interference with nervous impulse appears to us to be the most likely mechanism by which pineal tumours cause pubertas praecox, and this view is strengthened by the fact that we are still without conclusive evidence of a pineal endocrine function.

Midbrain and hypothalamic tumours.—The pathological description of the tumour found at autopsy places our first case in this group, and there are a few other cases in the literature.

Heuyer (10) in 1931 reported “un cas de macrogénitisme précoce liée à un épéndymogliome de la région mamillotubérale”. The patient was a boy of 6 who came under observation with a history of abnormal growth and sexual development from the age of 4 years. His height was 50 in. (max. normal 46.5 in.). The upper and lower measurements

were not given, but the trunk showed the greater relative development, the genital organs and pubic hair being well developed. He died after an exploration for pineal tumour. A tumour was found in about the same situation as in our case, and of a strictly limited nature, and had not caused destruction of hypothalamic nerve centres.

Horrax and Bailey (11) present another closely related case in which a boy began at the age of 3 years to develop pubic and axillary hair; within a year the external genitals developed to adult size and he became adipose. On examination at the age of 7 years his height was 56 in. (max. normal 48·8 in.); he was both muscular and adipose, and the ossification of the epiphyses corresponded to the age of 18 years. At autopsy a ganglioneuroma was found occupying the 3rd ventricle and attached to the infundibular region. Internal hydrocephalus was present.

Schmalz (31) reported another case. A boy aged 12 years died after a decompression for suspected cerebral tumour. His square build and developed shoulders and pelvic girdles gave him the appearance of adult build. Genital organs and pubic and axillary hair were well developed, and the eyebrows were strongly marked. A tumour of nerve elements was found arising from the floor of the 3rd ventricle with two cysts projecting into the lateral ventricles. Internal hydrocephalus was present.

Dods (12) has published a brief note of another case. A boy developed pubic hair at 3 years of age and by the age of 8 he showed the sexual development and secondary sexual characteristics of late adolescence. From his photograph he appears to resemble our first case with a relatively large upper measurement and well-marked eyebrows. At autopsy an astrocytoma of the floor of the 3rd ventricle was found.

Inflammation of the midbrain.—A very few cases have been reported with pubertas praecox. Thomas and Schaeffer (13) describe a boy of 12 who had an acute illness as a baby, followed by hydrocephalus and delayed mental development. With a later exacerbation of inflammation in the brain shown by headache and vomiting, the genital organs grew almost to adult size. There was no somatic

overgrowth. At autopsy inflammatory lesions were found in the floor of the 3rd ventricle, together with cervical pachymeningitis. The ventricles were dilated. Pubertas praecox has been found following encephalitis lethargica, as also has dystrophia adiposo-genitalis (Von Economo (14)).

Adrenal cortical tumours.—It is of very great interest to consider how closely our patients resembled the cases described in the literature associated with adrenal cortical tumour. Up to 1934 there were only nine cases (3) and (15 to 22) of sexual precocity in boys in which an adrenal cortical tumour had been demonstrated. To take two of the more recent cases, Fordyce and Evans (21) describe a boy in whom pubic hair appeared at the age of 6 months, with development of the penis. He had red hair, a deep-toned voice, and was abnormally strong. At the age of 2 years and 3 months the genital organs were developed to the size of an adult male, but the somatic growth was not comparable to our case, for his height was only 34 in. (max. normal 36 in.) and his weight 38 lb. (max. normal 31 lb.). The boy was shy and did not talk. Another difference was that the ossification of the bones was normal. A tumour the size of a small orange was removed from the position of the left suprarenal capsule. The boy died twelve hours after the operation. The tumour was one of the suprarenal cortex, and metastatic growths were present in the brain and in the liver.

Lisser (3) (23) in 1933 described the first successful removal of an adrenal cortical tumour in a boy. The patient resembled our case in every particular except in the absence of the mental characteristics and the presence of emissions. At the age of 5 years he was the size of a boy of 7 or 8 years old, the external genitals were like those of an adult, emissions were frequent, and erections occurred. Radiographic examination showed a degree of ossification normal for 11 or 12 years. The upper measurement was 2 in. greater than the lower, the voice was somewhat lower than normal; he did not make any advances to the other sex and was rather reticent and bashful. Following the removal of the tumour, the patient improved to some extent, nocturnal emissions ceased, erections occurred but rarely, and some of the mous-

tache and pubic hair vanished, but his somatic growth continued unabated. During the first year he grew $3\frac{3}{4}$ in., during the second $4\frac{1}{4}$, and during the third $3\frac{1}{2}$. The fact that operation did not check excessive growth at first suggested to Dr. Lissner the possibility of further cortical tumour. No evidence of this could be found, and in the following three and a half years he only grew 5 in., showing a slowing in the rate of growth. When examined aged $11\frac{1}{2}$, he had to shave the upper lip once a week and the beard once in two months. Genital organs were of adult size and pubic and axillary hair was plentiful. Erections were becoming less frequent and he was not very interested in the female sex. At the age of $12\frac{1}{2}$ years he was still in good health.

Von Kup (36) reports an interesting case of a boy with a malignant adenoma of the adrenal cortex. The autopsy findings were premature puberty, hypertrophy of the testes but no signs of spermatogenesis, hypertrophy of the epididymis and prostate, hypertrophy of the anterior lobe of the pituitary with an increase of eosinophil cells, abnormally small pineal gland, and hypertrophy of the acinous part of the pancreas with relatively few islets. He suggests that the increased activity of the adrenal cortex caused hypertrophy of the anterior lobe of the pituitary, which latter had an inhibiting action on the pineal gland and an accelerating effect on the development of the gonads.

Similar cases have been reported in little girls. Kepler and Dixon (35) report the case of a little girl who began to show precocious development at the age of 18 months. She grew rapidly, so that at the age of 23 months she was able to exchange dresses with her sister aged 5 years. The labia and clitoris enlarged and black hair appeared on the labia majora. At 19 months vaginal bleeding occurred for one day. Radiography showed the epiphyses to be developed to about the age of 6 years. A cortical adenoma of the left suprarenal gland was removed. A few months later she was in good health but the pubic hair had changed very little. She did not eat as heartily as before operation and she was much more composed and easier to handle, while no further menstrual periods occurred.

Tumours of the gonads.—Rowland and Parkes Weber (24) reported the case of a boy who was normal up to the age of 6 years, but who then grew so rapidly that by 9 years of age he appeared to be a grown man. The well-marked eyebrows, abundant hair, and muscular appearance were also present. A growth of the left testis was removed, which was found to arise from the interstitial cells.

Similar cases have been reported with reference to tumours of the ovary (see p. 139). These are usually arrhenoblastomas and very rarely granulosa-celled tumours.

Physiological pubertas praecox.—We have already pointed out that a child may show considerable exacerbation of growth and sexual development a year or even two or three years before puberty would normally occur, and that these children only differ in degree, as far as signs and symptoms are concerned, from the patients described above. Their subsequent development is normal, but they are mentioned here because they have a bearing on the problem as a whole.

Conclusion

These groups have been briefly described to demonstrate that pubertas praecox of apparently identical type is associated with a number of different conditions. When we analyse these conditions we find that the organs involved in pathological change, the pineal, the hypothalamus, the adrenal cortex, and the gonads, are all functionally and embryologically closely related to one another.

Pubertas praecox differs from most pathological conditions in that if it occurred at a normal epoch in life it would not be pathological at all. Endocrine research has shown that it is the anterior pituitary sex hormone which acts upon the gonads to produce the changes of puberty. The cases classed as physiological pubertas praecox show obvious hyperactivity of this pituitary-gonadal mechanism and only differ from the other types in degree. It seems reasonable to consider that a similar physiological mechanism is being activated in each group. Adrenal cortical hyperactivity, whether functional or due to new growth, upsets the normal androgen oestrogen ratio, and an abnormal production of these

hormones is probably the cause of the adrenal group of pubertas praecox. A similar explanation would cover the rare cases associated with tumours of the ovary and testis. It is not clear whether the pituitary is involved in the production of pubertas praecox in the adrenal and gonadal groups, but the following case suggests that pubertas praecox cannot be produced in the absence of a normally functioning pituitary gland. Raymond and Claude (27) describe the case of a boy of 10 years old who looked 13; he was obese and showed pubic hair, but the testes were abnormally small. Autopsy revealed a cystic glioma of the pineal producing considerable pressure atrophy of the pituitary. The adrenals contained nodular tumours, with microscopical evidence of hyperactivity of the cortex and medulla.

The evidence of an internal secretion of the pineal is extremely doubtful, but that it has some function in connection with sex is likely. Berblinger (25) points out the probability that the pineal exerts its effect by nervous influence on the hypothalamic centres and thence on the hypophysis. Direct pressure of a pineal tumour or indirect pressure through an increase of intracranial pressure on the hypothalamic nuclei cannot be discounted in most pineal tumours associated with pubertas praecox. We know that nerve fibres pass from the hypothalamus to the pars nervosa and pars intermedia, and that in all probability the hypothalamus and the posterior pituitary form a functional unit (39), so that a pineal influence upon the posterior pituitary would not be impossible. Furthermore, the hypothalamus is closely related to the sympathetic system, as shown by the researches of Cannon (5) and others, and sympathetic fibres from the carotid plexus can be traced to the anterior pituitary lobe (Dandy (26)). Thus the whole of the pituitary gland is connected by nervous influence to the hypothalamus, and it seems reasonable to suppose that the stimulus of a pineal tumour, or of a hypothalamic tumour, presses the trigger to fire the pituitary-gonadal mechanism of puberty.

In the ordinary way the hypothalamic centres probably control the activity of the pituitary gland to some extent, because primitive emotional reactions which are not de-

stroyed by isolating the cerebral cortex originate in that area, and emotional reactions act through the whole endocrine system, and this hypothalamic action on the pituitary must presumably be due to nervous influence. Direct pressure on the pituitary gland is never associated with pubertas praecox and the group of hypothalamic cases are of great theoretical interest because they show clearly that the anterior lobe of the pituitary as well as the posterior lobe must be in close functional association with the hypothalamus.

The mechanism of pubertas praecox would appear to be the abnormal production of androgens or oestrogens either due to hyperactivity of the normal pituitary-gonadal mechanism, stimulated perhaps by pineal or hypothalamic influence, or produced directly by the gonads or adrenal glands. If there is a connecting link between all these conditions it is probably furnished by hypothalamic control of the pituitary.

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CHAPTER 7

ADRENAL ENDOCRINE DISORDERS

THE functions of the adrenal cortex and its relation to the anterior lobe of the pituitary gland have already been described. The clinical results of the disturbances of these functions are very striking.

In foetal life over-activity of the adrenal cortex produces pseudo-hermaphroditism and in early childhood it results in premature sexual development with great muscularity and growth in boys, and precocious menstruation sometimes with excessive growth in girls (see Chapter 6).

After puberty, over-activity of the adrenal cortex in women causes virilism, that is, hirsutism, loss of sexual function, and a change towards the male habitus. This condition is known as the adrenogenital syndrome. The corresponding disorder in males, which is very much rarer, may show an over-development of male characteristics or, more rarely still, feminisation. Simple hypertrophy of the cortex, adenoma, carcinoma, and hypernephroma have been found in association with these symptoms and any of them may produce the syndrome. Adrenal cortical excess may pass at any time into deficiency, the most typical form of which is Addison's disease.

The Effect of Over-activity of the Adrenal Cortex in Foetal Life (Pseudo-hermaphroditism)

In the female the clitoris is enlarged, the vulva is more or less closed and resembles a scrotum, and the body approximates to the male type; the internal genital organs are female. Conversely, in males the external appearance of the body resembles a female whereas the internal genitals are

those of a male. True hermaphroditism in which both testis and ovary are present is a much rarer condition and is often associated with other anomalies.

An interesting case which illustrates the relation of the adrenals to pseudo-hermaphroditism is reported by Gold (1). A 13-year-old boy had been brought up as a girl owing to his feminine appearance. Recently he had complained of pain in the left side, wasting, and frequency of micturition. He was slightly built, showed abnormal breast development, a very short penis, and labia majora instead of a scrotum. A rudimentary vagina with the urethra emptying just above it was present. An exploratory laparotomy showed two inoperable retro-peritoneal tumours arising from adrenal tissue. Deep therapy was given during the next two years with reduction in the size of the tumour and relief of pain. After cessation of treatment a complete change took place, the voice became deeper, muscular development ensued, a moustache developed and he declared himself to be a boy. Two years later this development had progressed and a well-developed penis was present with a recognisable scrotum. The right testis was in the inguinal canal, the left testis could not be felt. The influence of treatment in this patient was remarkable, but in the majority of cases of pseudo-hermaphroditism no treatment is possible.

Young (2) has recently reported six cases of female pseudo-hermaphroditism in all of which the adrenals were examined and hyperplasia of the inner layer of the cortex was found to be present. Evidence is accumulating which links congenital anomalies with ante-natal endocrine dysfunction in the mother, and this is encouraging because the possibility of prevention will follow. For instance, a number of experiments by Dantachakoff (3), Greene (4) (5), Hamilton (6), Raynand (7) (8) give the following results. In guinea-pigs and mice, if the mother is treated with male hormone during pregnancy, the female young show externally a male habitus with a clitoris resembling a penis and a scrotum-like development of the space between the anus and clitoris. The ovaries are normal and the tubes and uterus more or less completely formed. The distal part of the vagina is completely missing

in animals whose mothers are given larger doses of male hormones. At the proximal end of the urethra a pair of glandular formations similar to the prostate is formed, as well as other organs which are similar histologically to the vesicular glands in males. Oestrogens tend to produce female characteristics in male embryos, but experiments are not very satisfactory because large doses cause abortion.

Effect of Adrenal Cortical Excess in Adolescent Males

In adolescence the condition resembles that found in *pubertas praecox*. The development of the epiphyses is advanced, so that the stature is short and stocky while the external genitalia are enlarged. Engelbach (9) describes a case which was probably due to functional disturbance of the adrenal gland, as no evidence of tumour was found. The appearance of the penis, which was very large, resembled that found in Plate No. 31, in which precocious development had been initiated by treatment.

Very rarely an entirely different syndrome, that of feminisation, occurs in males with adrenal cortical excess. Levy Simpson and Joll (10) report a case and describe five others from the literature. One was a boy of 15 years, originally described by Holl (11). He showed enlarged breasts with prominent pigmented nipples and suprapubic hair of feminine distribution. An irremovable adrenal tumour was found at operation.

Effect of Adrenal Cortical Excess in Adolescent Females (Adreno-genital Syndrome)

(*Synonyms* : suprarenal virilism ; hirsutism ; adrenal cortical syndrome)

Broster (12) has made a comprehensive study of this condition and classifies the adreno-genital syndrome into four groups :

- (1) Primary or prepubertal virilism.
- (2) Secondary or postpubertal virilism.
- (3) Achard-Thiers syndrome or pluriglandular group.

- (4) Postmenopausal virilism. (This is included for completeness but is outside the scope of this book.)

In the first group the normal changes do not take place at puberty ; instead the body contour alters towards the male type, hirsutism develops, the voice deepens, the breasts fail to develop, the clitoris enlarges, and as menstruation does not occur, a convincing picture of masculinisation is produced.

The second group is much more numerous, but as puberty changes have already taken place, masculinisation is not so complete, and patients showing minor degrees of the syndrome are not uncommon. Menstruation becomes irregular or ceases, hirsutism develops, and the bodily contour varies towards the male type to a less or greater degree.

An instructive case was described by Lawrence (13) :

A girl of 14 years gave the following history. The menstrual periods started at 10 years and 8 months and were normal until she was $12\frac{1}{2}$ years old, when menstruation ceased. When she was about 13 years old the voice became deeper and hair appeared on the arms, legs, abdomen, cheeks, and chin, and this steadily increased up to the time she came for examination when pubic hair extended to the umbilicus. Acne was present on face and chest. It is interesting to note that acne is very common in the adreno-genital syndrome as it is in hypogonadism (see p. 168), suggesting that a disturbance of the androgen-oestrogen production underlies its appearance. The clitoris was slightly enlarged. All investigations were negative and the patient was kept under observation for a year when an exploratory laparotomy was performed. The uterus was found to be small, the ovaries contained simple cysts and were sclerosed, the left kidney and adrenal body were normal to palpation, but the right adrenal could not be plainly felt. No significant change took place for five years, when she developed dyspnoea and tachycardia on effort, and it was found that the blood-pressure had risen to 140/80 mm. Hg. and the breasts had become atrophic. Seven months later an indefinite mass could be felt in the right flank and a pyelogram confirmed this finding. A rounded tumour of the right adrenal with the right kidney was removed at operation. Within two months of operation the patient's voice had regained a feminine quality ; the following month menstruation returned and has continued regularly since ; two years after operation the hypertrichosis had practically disappeared.

The points of particular interest in this case are the long history, the fact that a very small adrenal cortical tumour caused masculinisation, and the fact that the ovaries resumed function quickly and successfully although they had been found to be sclerosed six years before.

The third or pluriglandular group comprises a large number of cases which show signs of involvement of other endocrine glands. It includes amongst others the syndrome described by Achard and Thiers as "the diabetes of bearded women", which is outside the scope of this book. The chief symptoms are hypertrichosis of the male type on the face and menstrual disturbance, together with obesity, high blood-pressure, glycosuria, and other symptoms such as a red plethoric complexion, striae on the skin, kyphosis, and osteoporosis may be added, and the condition cannot then be distinguished from Cushing's syndrome, to be described later (p. 154). In our experience many more patients fall into this group of adreno-genital cases than into the first two groups combined. Many girls during adolescence show some of these symptoms, but all the conditions merge into one another and a series of patients could be found passing by almost imperceptible degree from the virile hirsute manly woman at one end of the scale to the fat, plethoric, hirsute woman of Cushing's syndrome at the other. We will give a few examples from our case sheets of the type of case which falls into this group in early adult life.

CASE No. 128.—Plate No. 33. This girl came under observation at the age of 12. The family history does not show any abnormal features; the father and mother are both short and stout but one brother is perfectly normal. The birth weight was $3\frac{1}{2}$ lb. and the mother had fits for twenty-four hours before she was born; after three months she developed well and walked and talked at the usual times; at school she was dull. She gradually became stout during childhood, reaching her present size by the time she was 14 years old. The menstrual periods started at 13, and have always been irregular; hair began to grow on the face at the age of 14, and has gradually increased.

On examination, she showed considerable general obesity, weighing about 15 stone. The eyebrows were well defined; a moustache, beard, and hair on the side of the face were present

and had to be shaved frequently ; the pubic hair reached the umbilicus and hair was present in large amount on thighs, legs, and the extensor aspects of the forearms. The blood-pressure was not raised. Radiography of the skull showed an abnormal degree of hyperostosis of the frontal bone. The patient has been under observation for fourteen years, without material change in her condition. Recently she has been investigated again with the following results. The B.M.R. was -6 and estimations of sugar, urea, potassium, sodium, and cholesterol in the serum were all within normal limits. Plasma chlorides were also normal and Volhard's water-balance test showed that there was no water retention.

The obesity, hirsutism, and irregular menstrual function form an obviously abnormal syndrome which may be attributed to adrenal or pituitary disorder, but it is of interest to note the lengthy course which has already been run. The cases of this type reported in the literature are generally those in which an adrenal tumour has been found, but it is well to remember that there are many patients like this, in whom the condition does not change over a very long period.

CASE NO. 129.—A similar but not so pronounced an example is shown in Plate No. 34. This girl of 14½ years was referred for obesity and hirsutism. She had always been plump and the periods, which had started at 13, had not become regular. She had recently suffered from headache.

On examination, there was a slight general adiposity for she weighed 151 lb. (max. normal 116), and the height was the mean normal of 62 in., while the appearance was mature for the age. The eyebrows were well defined, a moustache was present, while the pubic hair was of masculine distribution. The blood-pressure was 140/90 mm. Hg. A stereo-radiograph of the skull showed that it was large for the age, but otherwise nothing unusual was seen ; the epiphyseal development was advanced by about five years, the sigma reaction of the serum was negative, Volhard's water-balance test gave no evidence of water retention, and the visual fields were full. Sodium and potassium estimations in the serum were not done. The patient left the neighbourhood and no further history is available.

The appearance and hirsutism and the advanced development of the epiphyses form a resemblance to the cases of *pubertas praecox* (*e.g.* Plates No. 28, 29, 30), and stress the connection between the syndromes described in this and the previous chapter.

CASE NO. 127.—Plate No. 35. A young woman aged 22 years. The family history was normal except that one maternal aunt had had goitre. As a child she was plump. The menstrual periods started at the age of 13½ years but only occurred at three to six monthly intervals and lasted from one to two weeks. She complained of undue fatigue during the previous three years.

On examination, the patient was obese especially on the trunk, the height being 65 in. and the weight 172 lb. The eyebrows were well defined, and there was a masculine distribution of pubic hair. Some diffuse enlargement of the thyroid gland was present and the blood-pressure was unduly high, 170/110 mm. Hg. Pelvic examination did not show any abnormality. Radiographs of the skull and epiphyses were normal. Volhard's water-balance test showed that there was no retention of fluid but excretion was not quite as rapid as is usual. The B.M.R. was +5 (normal). The sigma reaction of the serum was negative. The estimation of the blood-urea, sugar, cholesterol, plasma chlorides, and serum sodium all gave normal figures but the serum potassium was raised to 31 mg. per 100 c.cm. The latter result, which was confirmed, is usually found in Addison's disease or hypo-cortical conditions, but this is another example of what has been frequently stressed, namely, the infinite variation of endocrine dissociations. The patient was instructed to take an 8-line Lawrence's diet and ½ oz. of salt daily. In five months the systolic blood-pressure had fallen to 120 mm. Hg. and the serum potassium figure to 15.5 mg. per cent; the weight had dropped 16 lb. and she felt much more energetic. The menstrual function had not changed and the patient ceased attendance before treatment directed to that had been given. See under Cushing's Syndrome for further discussion of this condition.

Cushing's Syndrome

(*Synonym* : pituitary basophilism)

It is most common in young adults and adolescents, particularly females.

Morbid Anatomy

The pituitary basophil adenoma originally described by Cushing (14) has not always been found, but a hyaline change in the basophil cells first described by Crooke (15) is present in most if not all cases of the syndrome. Hyperplasia of the adrenals is common.

Symptoms

The patient complains of fatigue, weakness, lumbar pains, rapidly acquired obesity, which is sometimes painful, of the face, neck, and trunk, with a red plethoric complexion and a dry skin on which lineae atrophicae of a red or purple colour may be found. The lower extremities are congested and the blood-pressure raised. Kyphosis is marked with osteoporosis of the skeleton and shortened stature. Amenorrhoea and reversal of secondary sex characters take place in women, ultimate impotence in men; in young men and women there is hypertrichosis of face and trunk, in adult males hair is diminished. Glycosuria, acrocyanosis, and oedema of legs are less often found.

We have, then, described two conditions, the adreno-genital syndrome and Cushing's syndrome, which are obviously very closely linked. The typical example of the first condition is a young woman with masculine build and hair distribution and loss of ovarian function. Cushing's syndrome shows similar hypertrichosis and sexual disability, combined with obesity, high blood-pressure, and plethora. The distinction between these conditions is neither clear pathologically nor clinically; the typical examples of both syndromes are rare and form either end of a scale which is filled by intermediate cases showing some of the symptoms of both. It is also of interest to note that many of the signs of Cushing's syndrome have been described already in relation to other pituitary syndromes, for example kyphosis, plethoric appearance, and striae.

Diagnosis

From the descriptions of the adreno-genital and Cushing's syndromes it will be realised that in most cases it is impossible to be certain of the cause of the clinical syndrome in any given patient. The presence of an adrenal tumour may be obvious or may be determined by the methods suggested on p. 138. Some authorities explore the adrenals to see if hypertrophy or a tumour is present, but we know from the experience of Broster (12) that many patients with severe

virilism show no enlargement of the adrenal, so that the size is not an index of pathogenicity. If a basophil change in the pituitary is the underlying cause it is impossible to demonstrate. Many of the tumours in the pituitary gland have been very small, and in fact it seems likely that in many cases tumour formation does not occur but that there is a hyaline change in the basophil cells.

There are two methods which in the future will probably help us to understand the varying mechanisms of these conditions: the estimation of the androgen-oestrogen ratio of the urine, and chemical investigations of the serum. At present research has not progressed sufficiently to give clear indications for treatment by either method.

It is of interest to note the different conditions which may cause reversal of sexual characteristics as listed by Kepler (16):

- (1) Adrenal tumour and hyperplasia.
- (2) Basophil pituitary tumour.
- (3) Hyperplasia of adrenal with thymic oat-celled tumour.
- (4) Arrhenoblastomas and, very rarely, granulosa-celled tumours of the ovary.

Therefore in rare instances we must bear in mind tumour of the ovary and thymus.

Treatment and Prognosis in the Adreno-genital and Cushing's Syndromes

The treatment varies with the cause. If the presence of an adrenal tumour can be demonstrated it should be removed, and if metastasis has not already taken place the result may be satisfactory. In groups 1 and 2 of the adreno-genital syndrome Broster (12) advocates removal of one adrenal gland if the clinical condition is severe. The results in his cases have varied, but generally hirsutism has been improved and sometimes psychological benefit experienced.

In most cases the treatment we adopt is symptomatic, as exemplified in Case No. 127 above. All obese patients are dieted; if the Na and K values of the serum are not normal,

more or less salt is suggested. Irregular menstruation is treated with gonadotropic preparations. In the mild examples of the syndrome some improvement is not infrequently obtained. The outlook in a typical Cushing's syndrome is usually poor, but the adreno-genital type run a more chronic course and some at least of the lesser examples of both syndromes remain unchanged for many years.

Discussion of the Various Syndromes described in this Chapter

A very interesting hypothesis which seeks to explain the underlying endocrine mechanism of all these syndromes has been suggested by Vines (12). Here the outline only of his arguments can be given and readers are referred to his full work. He finds by a special staining technique in a number of cases of virilism that a red granular material can be demonstrated in the cortical cells, and this reaction was obtained in 34 of 36 cases where adrenalectomy was performed for clinical virilism. He regards this staining reaction as a sign of androgenic activity of the cortical cells and finds a correlation between the presence of this substance and the presence of androgen in the adrenal gland, as demonstrated by the capon test. Vines then examined the adrenal gland in a large number of conditions as well as in the human embryo at different stages of development. From these researches and from parallel biochemical and hormonal investigations the following conclusions are drawn.

The initial determination of sex in the normal individual is the chromosomes of the parental germ cells, but endocrine factors during foetal development are capable of altering it. The mechanism of hormonal sex determination depends upon the production of androgenic and oestrogenic hormones at all stages of life. By the staining reaction it is shown that the first observed activity of the adrenal cortex is an androgenic phase common to both sexes in early foetal life, and it is suggested that the mechanism of hormonal sex determination is an adreno-pituitary interaction and that failure to control the female androgenic phase leads either to foetal masculinisation and pseudo-hermaphroditism or, if the androgen becomes dominant later, to adolescent virilism. In pituitary

basophilism (Cushing's syndrome) the relation of the adrenal to the pituitary is shown by the adrenal hypertrophy and the same or a similar syndrome is produced by adrenal cortical carcinoma. These conditions also demonstrate that the cortex possesses oestrogenic properties which can cause feminisation of the male. Vines says "that the adrenal cortex is a potentially bisexual accessory sex-gland largely controlled by the pituitary and capable of secreting simultaneously androgens or oestrogens the one or the other in excess. The method of pituitary control is by a hormone which is either prolan or perhaps more probably the adreno-tropic hormone."

This adreno-pituitary mechanism probably governs sexual development during foetal life and until puberty, when it becomes submerged by the activity of the gonads which have been matured under pituitary influence, the gonads producing both androgens and oestrogens also. In the reproductive period the pituitary-gonad relationship is the dominant mechanism, but in the abnormalities of this period of life, which have been described, it is the adreno-pituitary mechanism which is deranged. When later in life, owing to atrophy of the gonads, the gonad-pituitary mechanism fails to function, then the adreno-pituitary mechanism again occupies the dominant position, and cortical hyperplasia may be found, the androgenic element being usually more pronounced in women than the oestrogenic in men.

Whether the arguments on which this hypothesis is based are substantiated or not, it appears to clarify thought on the syndromes described in this chapter, forming a basis for research and observation in a series of puzzling conditions.

Addison's Disease

This condition, which is especially rare in children, is characterised by progressive weakness, low blood-pressure, and pigmentation of the skin and mucous membranes, resulting from disease of the adrenal glands.

Aetiology

It is most common between the ages of 20–40 years but Atkinson (17) has recently collected 40 cases occurring in childhood, 25 in boys and 15 in girls, the youngest being 7 days old.

Pathogenesis

There are two types of morbid change in the adrenal glands either of which may cause Addison's disease. The more common is bilateral tuberculosis affecting both the medulla and the cortex, the other is a simple sclerosis or atrophy of the adrenal cortex, at first leaving the medulla more or less intact, the disease developing in spite of the relatively normal medulla. Mills (18) gives a table of 192 cases compiled from the literature of which 34 were due to simple atrophy. Experimental and clinical evidence shows that lack of adrenal cortical hormone is the main cause of the characteristic syndrome. (See Chapter 2.)

Symptoms

An insidious onset with increasing weakness is most usually found, and marked asthenia may be present without any definite physical signs. Sooner or later, some or all of the following characteristics develop. Attacks of diarrhoea, sometimes accompanied by obstinate vomiting, or other gastro-intestinal symptoms occur. Pigmentation of the skin starts at first on the exposed parts and on parts normally pigmented and then spreads more generally, particularly where pressure is exerted. A sallow complexion develops early and later may become brown or almost black. Patchy pigmentation of the mucous membranes is common. Cardiac weakness with feeble pulse and a low blood-pressure lead to frequent complaint of giddiness and syncope. Wasting is present but is not usually extreme. Anaemia is not as a rule prominent but there may be a relative lymphocytosis. The temperature may be normal, subnormal, or raised, and in that connection the possibility of tuberculous disease of the adrenals or coincident pulmonary tuberculosis must be

remembered. Headache and pain in the back are often present.

The downward course of the disease is usually checked by occasional remissions, but on the other hand acute crises of symptoms are a characteristic feature and occur from time to time. In the crises the patients resemble the condition found in acute surgical shock, exhaustion is extreme, the pulse is fast and feeble, the blood-pressure is very low, and vomiting may be almost continuous. The colour of the skin may be seen to darken from day to day and a black ring may appear around the mouth. The hair loses all lustre, becoming dry. Changes in the blood show a rise in urea and a fall in sugar. Dehydration occurs, for in Addison's disease there is a reversal of the normal sodium and potassium balance, with an excretion of the former and a retention of the latter salt. Death often occurs in the crises of the disease, but apart from that, sudden death is not infrequent and may be unexpected. The usual duration of an untreated case varies from a few months to a few years, and a few well-authenticated cases of spontaneous recovery have been reported in adults.

Diagnosis

In the early stages correct diagnosis in a child is unlikely, as more usual causes of chronic ill health such as abdominal or pulmonary tuberculosis would be first suspected, but Addison's disease may of course be present as an extension of tuberculous disease from elsewhere. Marked asthenia without other physical cause in the presence of pigmentation suggests Addison's disease. Radiography of the renal regions may show calcification. It has been shown by Thorn (19) and others that adrenal cortical extract in large doses causes a retention of sodium and an excretion of potassium salts. In early cases this may be used as a means of diagnosis, and is more reliable than the bare estimation of the sodium and potassium in the blood, for it is well recognised that the sodium and potassium concentrations are not necessarily an indication of the clinical picture. The deprivation of salt may precipitate an adrenal crisis and

the response to treatment with cortical extract is often of value in diagnosis.

Treatment and Prognosis

General care of health and the avoidance of stress and strain is the first essential of treatment, which must be considered further under the headings maintenance treatment and treatment of crisis.

Maintenance Treatment with Cortical Extract and Sodium Salts

Since the preparation of potent adrenal cortical extracts (see Chapter 2) the treatment of Addison's disease has become more satisfactory. The extract is given by intramuscular injection and an adequate dose determined for each patient by observing the general condition and the blood-pressure, and by estimating the sodium, potassium, and blood-sugar in the serum. About 12 g. of sodium chloride and 4 g. of sodium citrate are given daily, because the extract is not sufficiently powerful to keep the electrolyte balance of the blood steady and a loss of sodium salts occurs.

A low potassium diet is advisable, which is obtained to some extent by restricting potatoes and green vegetables. A diet which is very low in potassium is described by De Wesselow and Thompson (20) and has been used in treatment. It is monotonous and unpleasing and in our experience not easily tolerated by a sick person. Patients may sometimes be kept in health by sodium salts alone but extract will be required during crises. Extract alone will also maintain patients in health but large doses are required. In the same way as insulin it is necessary to increase the dose of extract during infection. Thompson (21) gives a recent account of treatment in seven patients with well-marked Addison's disease over a considerable period. Of these patients four are living and have received treatment for one to three and a quarter years, while three of them are able to carry out their ordinary duties. The youngest, a boy of 18, was the most difficult to treat, and in his case the development of adrenal crisis could not be prevented.

Maintenance Treatment with Desoxycorticosterone Acetate

In 1937 Steiger and Reichstein (22) finally isolated a substance which they called corticosterone from adrenal cortex and which is potent when tested on adrenalectomised rats. The same workers have synthesised a related compound desoxycorticosterone and in the form of the acetate it is now available for clinical use. Levy Simpson (23) suggests that 5 mg. is equivalent to 10 c.cm. of cortical extract (Cortin) in the treatment of Addison's disease. The use of this substance has considerable advantages compared with cortical extracts. Its action on the electrolyte balance is very powerful causing a retention of sodium and excretion of potassium. For this reason sodium salts need not be given with it, in fact if they are given oedema will develop, and if sodium retention is excessive, congestive heart failure may occur. It causes a considerable rise of blood-pressure but there is little or no effect on the carbohydrate metabolism and is not a complete substitute for the internal secretion of the adrenal gland. The best method of use of cortical extract and desoxycorticosterone has yet to be determined. Our present practice is primarily to use desoxycorticosterone acetate (prepared by Organon Laboratories) determining the daily maintenance dose as described above, and then giving in addition a small dose of a potent cortical extract. One patient who has been maintained in good health for several years is taking 10 mg. of desoxycorticosterone acetate and 0.5 c.cm. of cortical extract (Eucortone) daily.¹ The addition of sodium salts is not required. The insertion of tablets of desoxycorticosterone subcutaneously is said to be as effective as daily injections and suggests itself as a method for use in children. It remains for the future to show the relative value of these various methods of treatment.

Treatment of Crisis

An adrenal crisis is a serious medical emergency and must be treated immediately and energetically. The patient should

¹ This patient has since died during a second adrenal crisis. During the first adrenal crisis she was given 4275 g. of adrenal cortex daily as described p. 163. Autopsy showed both adrenal glands almost destroyed by tuberculosis.

be given hourly doses of cortical extract intramuscularly or intravenously ; the doses will depend on the extract used but very large doses may be required. We have given hourly doses, for nineteen hours out of the twenty-four, of 3 c.cm. of an extract containing 75 g. of cortex per c.cm. or a daily dose of 4275 grams of adrenal cortex. In this instance the dose had to be continued for several days before the symptoms of crisis began to diminish. There is no danger of an overdose, and at the same time normal saline and glucose 5 per cent should be given intravenously until vomiting stops. This may be extremely difficult owing to collapse of the veins. Sodium citrate is valuable during a crisis because it can often be taken by the mouth, when sodium chloride causes vomiting. A saturated solution should be prepared and the nurse instructed to give it in small doses in fruit or other drinks. In this way as much as 2 oz. of the salt by weight can sometimes be given in the twenty-four hours. It replaces sodium and also raises the alkali reserve.

It is probable that desoxycorticosterone acetate will also largely replace cortical extract in treating crisis. The action on the electrolyte balance will obviate the necessity of giving sodium salts and will probably greatly reduce the large doses of extract required. With desoxycorticosterone the danger of overdose with oedema and heart failure must be remembered. We have already treated some milder cases of adrenal crisis with this substance alone, but at present cortical extract is the safer remedy.

The prognosis has been greatly improved by treatment and the treatment of adrenal crisis is particularly successful. While a number of patients can be maintained in health for considerable periods, the ultimate prognosis is still poor, especially when tuberculosis is the under-lying factor.

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CHAPTER 8

HYPOGONADISM (ADOLESCENCE) : HYPOGONADISM (CHILDHOOD) : IMPERFECT DESCENT OF THE TESTIS : TREATMENT OF ACNE VULGARIS

Primary Non-adipose Hypogonadism

(*Synonym* : eunuchoidism)

ENGELBACH (1) has described a clinical entity under this heading, which, when present in a well-developed form, is identical with the condition resulting from castration in early life ; the individual grows tall and thin, secondary sexual characters do not develop, a lack of initiative results, and the persistence of childish emotional reactions leads frequently to nervous disorder. From observation of a number of cases we have no doubt of the existence of this syndrome. In males, genital under-development or cryptorchidism is usually found, and corresponding abnormality is present in the female sex but is naturally not so obvious.

Engelbach discusses the question, which has also interested us very much, of the pathology of the syndrome. Castration in early life, before the epiphyses have joined, produces the same condition, but this is not a definite proof that a gonadal defect is always the primary cause in these cases, where castration has not been performed, because the gonads are dependent for growth and maturation on the anterior lobe of the pituitary. It would seem possible for a break in the pituitary-gonadal chain to produce the same result whether the gonads or the pituitary formed the broken link. It is quite true that the gonads are obviously abnormal in many male cases, but this is the case in other pituitary conditions. For the present we have adopted Engelbach's term to describe this syndrome, but we think that it may in the future be

classified as another example of pituitary dissociation of function. The growth defect described in Chapter 5 is due to lack of anterior pituitary growth hormone, and it is interesting to speculate that hypogonadism may be due primarily to lack of anterior pituitary sex hormone. There is much clinical evidence linking primary hypogonadism with pituitary syndromes. In the hypopituitary growth syndrome the patients are usually thin, and later show gonadal defects. If, as sometimes happens, the hypogonadal patient is not typical, and instead of being tall is just below normal height, it becomes difficult to know whether to classify him as a case of primary hypogonadism or pituitary growth defect of mild degree with secondary hypogonadism. As in all endocrine syndromes, the well-established case is relatively rare, the lesser one more common, merging into related conditions. We have noted other evidence of connection with pituitary function, such as the presence of striae on the skin, the history of having been fat as a child, or the presence of hypothalamic symptoms such as narcolepsy. Perhaps the chief reason which has led us to suggest that this may be a pituitary syndrome is the fact that it occurs not only in adolescence, when the lack of gonadal secretion is obvious, but also in childhood. We first suspected that this condition could be found in childhood from the histories of the established cases, for it usually appeared that these patients had always been tall and thin, and that the condition had not suddenly developed at puberty. On looking for such a syndrome in children it was found to be present and will be described below.

There is another condition which appears to have obvious connection with hypogonadism and this is Von Bergmann's (2) pituitary emaciation. This syndrome is described in adolescent females and is characterised by a tall build, sexual dysfunction, slowly progressing emaciation, and general ill-health. From the published description of these cases we can see no difference between them and the more severe examples of the syndrome under discussion, and this will appear clearly in the description of our cases. Kunstadter (3) and others wish to include this latter condition

under pituitary disorder, arguing on the same lines as we have done and pointing out the resemblance of pituitary emaciation to Simmonds's cachexia, from which it differs by not ending fatally.

There is one further point which should be made clear. In general medical literature and even in endocrinological journals many papers will be found describing cases, from one point of view or another, under such general terms as "eunuchoidism" or hypogonadism, without any effort being made to define what is meant and often including a variety of clinical conditions. Now it has been pointed out elsewhere in this book that eunuchoidism, i.e. the result of a deficient gonadal secretion, may result from several varieties of pituitary and thyroid disease, but these are not under discussion; here we are concerned with one clinical entity which in the past has been regarded as due to primary gonadal defect but which may be classified in the future under pituitary disorder.

Signs and Symptoms in Adolescence

These cases show in part or in whole the symptoms and signs which follow castration in childhood, i.e. overgrowth of the long bones with consequent slender build, poor muscular development and thinness, late union of the epiphyses, hypoplasia of the accessory genitalia, and imperfect development of the secondary sex characters. Castration in adult life shows of course a different picture; as the epiphyses have fused, no effect on stature appears and adiposity, not thinness, is the rule. The majority of the primary hypogonadal cases also put on weight after the age of 25 years. Complete castration either from trauma or disease in early childhood is of course very rare and most of the patients in the primary hypogonadal group have some sexual function, so that partial examples of the syndrome are more common than the well-developed case.

The characteristic picture of a patient is as follows. He or she is an individual above the normal height, in whom the lower measurement exceeds the upper measurement and

the span exceeds the height, both to an abnormal degree, giving a long thin build with very poor muscular development. The weight may be so much below normal that the patient is emaciated. The head, chest, and abdomen show small measurements and the face retains the infantile characters, with a failure in development of the maxillae tending to anterior angulation of the face with a receding lower jaw.



PLATE 36. CASE No. 55.—Age 15½ years. Shows typical facies.

The upper central incisors are large while the lateral incisors are small or absent. The fingers and toes are long owing to the delayed closure of the epiphyses, and the hands are the opposite type to the short spatulate hands of the patient with hypergenitalism. The skin is smooth and velvety and acne is often present on the face and trunk. In males the skin is hairless, in females there may be slight hirsutism and pubic hair of male distribution. According to the degree of defect the sex characters are deficient or absent. In males the external genitalia are very small, or cryptorchidism may be present. In some cases the external genitals may be practi-

cally normal but signs of hypogonadism may show in the measurements and imperfect development of secondary sexual characteristics, or it may be found that erections and emissions are infrequent. In the female menstrual function usually starts late and remains irregular; in very severe examples there is complete amenorrhoea. The internal genitalia show varying degrees of under-development, and the breasts are undeveloped; the build resembles that of a boy lacking the female contours. The voice in both sexes often permanently retains the childish character in varying degree. See Plates No. 37 to 44.

In hypogonadism there is a normal or even possibly an excess of growth hormones of pituitary and thyroid so that growth in early life is excessive, while the defect of gonadal secretion leads to delay in epiphyseal closure so that growth can continue for a longer period than normal. We have seen a case with ununited epiphyses in middle age and many have been reported. It follows that, in very well-developed instances of the syndrome, eunuchoid gigantism may result, of which the following patient is a mild example.

CASE No. A3.—A man aged 65 years came to hospital complaining of dyspepsia. The measurements were as follows:

Height	74.75 in.	Upper Measurement	29.75 in.
Span	85.0 „	Weight	223.0 lb.
Lower Measurement	45.0 „		

It will be noticed that the span exceeds the height by 10.25 in. while the lower measurement exceeds the upper by 15.25 in. These are the highest figures we have recorded. The external genitals were very small, the pubic hair scanty, the voice high-pitched, and he had never shaved. The weight was high, but many of these cases become obese later in life.

Another extremely important point is the fact that these patients usually complain of symptoms which are not obviously connected with the endocrine glands, but refer to the nervous, gastro-intestinal, or circulatory systems. The nervous symptoms are the most prominent and are present to some degree in almost every patient, nervousness, lack of confidence, and the persistence of childish emotional reaction

being constantly found ; migraine or other forms of headache are very frequent, and fits, spasmodic torticollis, and habit spasm have all been noted. The resulting condition may be so severe as to prevent the individual earning a living and ordinary social contact in work and play is rendered difficult and unsatisfactory. In the male sex the feeling of inferiority is accentuated by the sexual disability ; in women, although sexual frigidity and lack of libido are usually present, this is not regarded as of much importance, if recognised at all, and does not give rise to the same amount of mental distress. But in both sexes a lack of initiative and energy often leads to a diagnosis of neurasthenia which is likely to be attached to the patient for life. Circulatory symptoms add to the nervous disability ; tachycardia is frequently complained of and the patients have little capacity for physical effort, falling into the group called by Lewis " effort syndrome ".

Abdominal symptoms are often present, either apparently gastric in origin with attacks of pain and vomiting, or intestinal with symptoms suggestive of mucous colitis or chronic appendicitis, and it is worth noting that gastric and duodenal ulcers are more common in the long thin type of individual.

Proverbially the hypogonadal type of stature has been associated with tuberculosis, and investigation by one of us (F. W. T.), has confirmed this observation, but on the other hand tuberculosis is very often diagnosed when it is not present because of the ill-nourished appearance of the patient. Diagnosis is further rendered difficult by the fact that patients with hypogonadism often have a slightly raised temperature which may continue for long periods. Two adolescent cases will be described which illustrate most of the important points.

CASE NO. 54.—Plate No. 37. This patient is a girl aged 16½ years who was brought to us for nervous symptoms. She was of a retiring disposition with a childish emotional reaction and showed no interest in the other sex. There was a habit spasm of the face but the intelligence was normal. Menstruation had not started.

On examination, she was of a slight thin build with scanty

pubic hair, poor mammary development, and acne on the face. The measurements compared with the normal were as follows :

Case No. 54	Patient	Normal
Head	20·5 in.	21·7 in.
Chest	29·0 „	29·6 „
Abdomen	23·5 „	25·0 „
Span	69·0 „	61–66 in.
Height	65·0 „	61·4–65·6 in.
Lower Measurement .	35·0 „	30·0–33·0 „
Upper Measurement .	30·0 „	30·0–33·0 „
Weight	101·0 lb.	102·0–126·0 lb.

The typical hypogonadal features are present, the span exceeding the height by 4 in., the lower measurement the upper by 5 in., while the weight is below normal. Osseous development and a stereo-radiograph of the skull were normal. The sigma reaction of the serum was negative. No family history was available as she was an adopted child. The patient was treated with Antuitrin S. (see p. 178) and posterior pituitary extract by injection and within two months the menstrual periods began and became regular within a year. During the second year treatment was not given so regularly and nervous symptoms were more prominent for some months. At the end of that time treatment with Progynon was given, and after about six months the periods became regular without pain, the mental condition had much improved, the chest measurement had increased 2 in., the abdominal measurement 1 in., and the weight 9 lb. From then onwards progress was uninterrupted without treatment; she worked steadily as a typist, and when seen at the age of 21½ years looked the picture of health, and menstrual function was normal. Weight had increased to 129 lb., but of course the statural abnormality persisted, for the lower measurement was 6 in. longer than the upper and the span 3½ in. longer than the height.

This patient was an example of the syndrome which greatly improved under treatment, for the difference in mentality and general ability was particularly noticeable. The epiphyses showed no retardation by radiographic examination. We have noticed this in other cases in which sexual function was obviously deficient and it puts out of court, in some of these patients, the accepted explanation of the over-growth of the long bones, and as an alternative suggestion, it seems likely that there is an over-production of growth hormone.

CASE NO. 57.—A boy aged $13\frac{1}{2}$ years came to hospital with the history of having had four epileptic fits within the preceding four months. The measurements compared with the normal were as follows :

Case No. 57	Patient	Normal
Head	20.5 in.	21.4 in.
Chest	28.0 "	28.0 "
Abdomen	27.0 "	24.6 "
Span	64.5 "	58.0-62.4 in.
Height	60.0 "	56.9-60.9 "
Lower Measurement .	33.5 "	28.5-31.3 "
Upper Measurement .	26.5 "	27.7-30.5 "
Weight	89.0 lb.	96.0 lb.

They show that the span is $4\frac{1}{2}$ in. longer than the height, that there is an exceptional difference of 7 in. between the upper and lower measurements, and that the weight is low. The genital organs were small and the left testis was undescended. In this case also the epiphyses were normally developed. He was treated with injections of Antuitrin S. weekly for nine months, when he ceased attendance, no fits having been experienced for five months. He reappeared two and a half years later because fits had recurred. His age was now $16\frac{1}{2}$ years and the genitals were unchanged. He was given Pregnyl 500 rat units weekly ; in ten months the penis and testes became normal, but the pubic hair still showed a feminine distribution and axillary hair was not present. During this year he had only two fits and treatment was then stopped. Seen again aged $18\frac{1}{2}$ years, he had had no fits for a year, erections and emissions were present, he shaved once a week, and the weight was 142 lb. There was a difference of 8 in. between the upper and lower measurements and the span exceeded the height by 3 in.

These two patients show typical symptoms and signs, nervousness, habit spasm, together with tall thin build, poor muscular and delayed sexual development. In a well-developed case it is an unmistakable picture, but nevertheless the primary endocrine nature of the trouble is often overlooked and a diagnosis such as anaemia or tuberculosis made. The female patients form yet another section of the large class who attend the gynaecologist for menstrual disorders, and if proper endocrine treatment is not given, later on they form part of the chronic neurasthenic section of the popula-

tion. If the characteristics are grasped, minor degrees of the syndrome will be found to be extremely common and will often shed light on problems otherwise obscure, and indicate the line of treatment that is required.

Other Instructive Points from our Case Sheets

We have not noticed many facts of interest in the family history except the presence of fits and migraine in some cases. In the personal history of the patient, headache, migraine, or other form of "bilious attack" is usually noted. An interesting point was noted in the history of a nervous girl of 16 years (Case No. 58) who was seen for irregular and painful menstruation :

At the age of 4 years she was so fat that it was thought necessary for her to see a children's specialist. A photograph at the time shows a child with trunk obesity. At the age of 13 years she became extremely thin and grew very fast, to become at 16 years the picture of a typical hypogonad : height $68\frac{1}{2}$ in. with a lower measurement $3\frac{1}{2}$ in. longer than the upper, poor mammary development, small head and chest, and large upper central and small lateral incisors. Treatment over several years resulted in satisfactory mental and physical improvement, but the particular interest lies in the early indication of a glandular imbalance of a different type to that which subsequently developed.

Another patient showed a hypothalamic-hypophyseal sign, that of dropping asleep :

He was a boy of 17 years who had felt unduly fatigued for a year ; recently he had begun to eat voraciously and to fall asleep at odd times. The height was 70 in. and the span 72 in., while the lower measurement at $38\frac{1}{2}$ in. exceeded the upper by no less than 7 in. The weight was only 129 lb. ; genital organs were normal, but erections were occasional ; emissions did not occur, and the pubic hair showed a feminine distribution. The practice of routine measurement called our attention to the probable diagnosis of hypogonadism, which might otherwise have been missed. He was treated with Antuitrin S. over a period of six months ; the general condition improved, the symptoms disappeared and he ceased attendance, sexual function not having become normal. On enquiry several years later he was found to be serving in the Navy.

The following case illustrates the relation which we have already mentioned between hypogonadism and the condition termed pituitary emaciation.

CASE No. A1.—A woman of 42 (Plate No. 39) complained of pain in the abdomen and left hip and of chronic emaciation which had lately become more extreme.

She was one of twins (dissimilar) and had always been very thin; sexual development remained infantile, but at the age of 16 years menstruation occurred for a few months and then stopped completely until the age of 37 years, when it occurred every three weeks for six months.

On examination, the plate illustrates the extraordinary spectacle of emaciation presented by this patient. The measurements are of interest for they are absolutely typical, showing a small head, a span considerably longer than the height, and a lower measurement 4 in. longer than the upper.

Head	20.25 in.	Height	66.5 in.
Chest	25.0 „	Lower Measurement	35.25 „
Abdomen	23.0 „	Upper Measurement	31.25 „
Span	70.0 „	Weight	79.0 lb.

For many years her weight had not exceeded 84 lb., but as well as emaciation, she showed other characteristic signs; the voice was like that of a child, there was no mammary development, pubic hair was scanty and the external genitalia were infantile in type, the uterus was small when felt per rectum. Despite the puny development, which had never been materially different, she had worked continuously as a dressmaker. Intelligence was normal but the general outlook was childish and facile. The extremely youthful appearance of the face is characteristic of primary hypogonadism and contrasts with almost all other endocrine conditions which are associated with premature ageing.

For further investigation she was admitted to hospital; the sigma reaction of the blood-serum was negative, the B.M.R. was +22. She complained of pain in the left hip but a radiograph of the joint was normal. In the plate it will be seen that she is standing badly, and ultimately the reason was found to be a retro-peritoneal staphylococcal abscess (probably arising as a peri-renal abscess from blood-borne infection). After drainage the general condition improved considerably; she gained about 2 stone in weight, and the menstrual periods, which had only been seen for a few months five years previously, became regular each month.

Fifteen months after operation the weight was 92 lb. compared

with 79 lb. when she first attended, so that she still remained thin. The abscess cavity had healed and the general condition improved; menstrual periods were regular every month, but were extremely painful and preceded by intense vulval irritation, and gave rise to much mental distress.

The long history of emaciation is unusual and instructive; at the age of puberty she might have been classed as Simmonds's disease, and then, as a fatal termination did not result, the diagnosis might well have been changed to Von Bergmann's pituitary emaciation. At the age of 25 adiposity would have been expected to supervene, but on the contrary, she remained thin up to the age of 42 years. If it had not been for the pain of the staphylococcal abscess, she would not have come up to hospital, and that was the cause of the raised B.M.R. and the more recent loss of weight. It is difficult to account for the start of menstrual function after drainage of the abscess, but the extreme pain is probably associated with the infantile type of uterus and the intense irritation suggests a menopausal symptom.

The following case is quoted to show the more usual type of history, where adiposity develops at about the age of 25 years.

CASE No. A2.—Plate No. 42. At 10 years old the patient was said to be very thin and remained in the same condition until he was 25 years old when he started to put on weight. When seen two years later a mild degree of obesity was present for he weighed 180 lb. The span was 7 in. longer than the height, the lower measurement $4\frac{3}{4}$ in. longer than the upper. He had a high-pitched voice, scanty pubic hair, very small genital organs, and shaved once a month. The typically feminine contour is well shown in the plate, and two other signs associated with pituitary dysfunction were present, a finely wrinkled skin of the face and striae on the thighs.

Examination of Sexual Function in the Adolescent Girl

Many of the menstrual disturbances of adolescence, including examples of primary and secondary amenorrhoea, are found under the heading of primary hypogonadism, but the methods of examination described below are the same whatever endocrine disorder underlies the sexual disability.

Whenever possible we treat these cases in conjunction with the gynaecologist. Meaker (6) states that the menstrual function should be established, regular, and almost painless before the 15th birthday ; if not by the 16th birthday, the patient is an emergency case. We heartily endorse this opinion. If a patient has not menstruated by the 15th birthday we suggest an examination of the pelvic organs under an anaesthetic. Meaker (6) has tabulated some valuable signs of female genital hypoplasia, which are helpful in this examination :

- (1) The cervix may be long and conical with a pin-point os externum ; it may be anteflexed with or without retroversion of the uterus, which may be small or of normal size.
- (2) The myometrium is hypoplastic, consisting of 50 per cent of connective tissue and 50 per cent of muscle, while in the normal uterus the muscle is 90 per cent. Ovaries of infantile type are long and narrow and lobulated, and after puberty they often contain atretic follicles.
- (3) Vulval hypoplasia connotes an arrest in the internal organs, but the reverse is not true.
- (4) It is of value to measure the uterine index, for in the uterus of a new-born infant the cervix is two-thirds the total length, while in a normal adult it constitutes one-third. The infantile proportion usually persists until the 10th birthday, and rapid development takes place in the 13th, 14th, and 15th years to attain adult proportions at the age of 19 years. The ratio of the cervix to the total length of the uterus is an indication of the degree of differential development which the female reproductive organs have reached.

Further very valuable information on ovarian activity may be obtained by examining pipette samples of the vaginal mucous membrane from the posterior fornix. On the basis of the vaginal smear Shorr (7) divides cases into three groups, the first characterised by a constant atrophic smear, showing absence of oestrogen, the second group showing evidence of

subnormal activity, and the third group showing irregular cyclic vaginal smear changes reflecting periodic ovarian activity not sufficient to induce menstruation. The change in the vaginal smear may be used to check the effect of treatment.

There is also a very useful chemical method of investigating sexual development. Progesterone is produced after the follicle has matured and this is excreted in the urine as sodium pregnanediol glycuronide and can be extracted and estimated during the luteal phase of the menstrual cycle.

If pregnanediol is present in significant amount, it shows that ovulation has taken place. This test also can be used as a check on treatment. The estimation is made on a twenty-four-hour specimen of urine by a biochemist.

In the adolescent the microscopical examination of the endometrium is sometimes of service. The appearance of the various phases of the cycle is well known, and if the characteristic features of the luteal and secretory phases can be demonstrated, then presumptive evidence of ovulation and normal ovarian function can be obtained.

The examination of the sexual organs must not divert attention from the patient as a whole, and by means of a careful history and physical examination possible complicating factors such as focal sepsis, anaemia, or tuberculosis must be excluded. These might reduce or inhibit endocrine secretion.

Treatment of Sexual Hypofunction in the Adolescent Female

The remarks in this section apply equally to patients suffering from pituitary obesity and hypopituitarism, where these conditions are associated with genital under-development. The best method of treatment has not been determined, and widely differing proposals are current. But we would emphasise one point, the necessity of treating these patients at an early stage and not letting "nature take its course", as is so frequently advocated, with the result of permanent impairment of the reproductive function.

The main point at issue is whether to use substitution treatment with ovarian hormones,¹ or stimulating treatment with pituitary gonadotropic hormones. For the latter may

¹ Stilboestrol is the oestrogenic agent now most widely in use.

be substituted various preparations which do not come from the pituitary gland but which have similar actions. In this class are the follicle-stimulating substances extracted from pregnant mares' serum and the pregnancy urine preparations which are mainly luteinising in action. Our opinion, based on the facts in the physiology section, is that ovarian function is best stimulated by a proper balance of the follicle-stimulating and luteinising hormones of the pituitary gland, but the best method of doing this has yet to be determined. As seen above in the description of Case No. 54, which was treated a good many years ago, we formerly used the pregnancy urine preparations (chorionic gonadotropin) apparently with some success. It is now generally thought that these do not stimulate the follicle of the human ovary and therefore we no longer use them primarily. We remain, however, a little doubtful whether this statement is quite true because of apparent clinical result in many cases and because of the following pertinent observation.

Case No. 58, quoted above (p. 173), was treated for a considerable time with these preparations only, and subsequently was operated on for acute appendicitis by the late Mr. J. L. Joyce. He reported that the uterus and the ovaries were the size of a multiparous and not a nulliparous woman. The ovaries also contained cysts. Considering the history and appearance of the patient, it is reasonable to assume that the abnormal size of the organs had been caused by treatment: unfortunately uterine measurement had not been made before treatment. As there are now preparations which are known to stimulate the ovarian follicle, it is preferable to use them. At present we are using the follicle-stimulating factor which is obtained from pregnant mares' serum and marketed under various trade names. The one we have used is Serogan. We give 250 i.u. of Serogan two or three times weekly for two weeks followed by one week of Pregnyl 500 rat units twice weekly. After a week's interval we start another course; if unsuccessful, the dose of Serogan is increased. This treatment is particularly useful for the cases of secondary amenorrhoea which are not uncommon in the pituitary obesity, thyro-pituitary, hypo-

gonadal and hypopituitary groups. When examination does not show any gross abnormality of the pelvic organs, this treatment is frequently followed by regular menstruation. The treatment is also useful when menstruation is scanty or painful, and when puberty changes are delayed, without gross changes in the pelvic organs.

The cases of primary amenorrhoea occurring in these endocrine groups may be treated in the same way. Even where the uterus is of markedly infantile type, success may be obtained, but if it is not forthcoming, and particularly if the organs are very undeveloped, ovarian hormones are used. There is no doubt that ovarian hormones cause growth of the uterus, as in the case reported on p. 107. Large doses should be used such as Progynon oleosum forte (oestradiol benzoate) 50,000 i.u. two or three times weekly for two weeks in each month, with a dose of 2000-5000 i.u. by the mouth all the time; then when some uterine development has been obtained, as shown by pelvic examination or by vaginal smear, the treatment with follicle-stimulating substances may be tried again. We do not continue this ovarian treatment for more than three or four months. Lissner (4) reports a typical severe case which was treated with ovarian preparations for three years with gradual development of normal sexual characteristics and function. Shorr (7) advocates this type of treatment for cases of primary amenorrhoea. He gives oestrogenic hormone for two weeks of each month, using that amount of hormone which will transform the atrophic vaginal smear to the cornified follicular type. When treatment is stopped, a pseudo-menstruation will occur after about five days. He states that repetition will produce satisfactory development of secondary characteristics and enlargement of the uterus, and that after two years' treatment secondary sex characters will persist. Daily doses of 2000-5000 i.u. are required intramuscularly, or fifteen times this dose orally during the fortnightly period of treatment. Progesterone may be alternated after the oestrogen treatment, but it is not essential.

We have not given oestrogen in this way, but in hypopituitarism of the Lorain-Levi type in patients after the age

of puberty, it can be very useful. The induction of secondary sexual characteristics and the maintenance of regular bleeding may have a profound psychical effect on the patient and render a maladapted person able to live a useful life. A description of the treatment of several patients on these lines is given in a recent article (8). If the method is used it would be wise to give a period of rest occasionally to prevent profound effects on other endocrine organs. We should remember our ignorance of the ultimate result of prolonged treatment with these powerful hormones. The use of ovarian hormone by pellet implantation in these cases reduces the trouble and expense of treatment, but it is not practicable in this country at the moment because of the difficulty of obtaining pellets.

Treatment of Sexual Hypofunction in the Adolescent Male

In these patients who do not respond to gonadotropic preparations, or who come under observation in early adult life, treatment with testosterone should be used. Testosterone is an extremely potent androgen prepared from cholesterol. Esterification activates the hormone by retarding the rate of absorption and elimination, so that testosterone is used in the form of testosterone propionate. A large number of reports of treatment are available in the literature. Kenyon (5) reports the treatment of four adult eunuchoid patients with 25 mg. daily of testosterone propionate subcutaneously 5-7 times weekly for 28-99 days, and three of these had smaller doses for a further period. There was in all of the patients an early increase in erections and an enlargement of the prostate, in three an enlargement of the penis with an increase in sexual hair, in two a deepening of the voice. The influence of the treatment on the testes themselves was doubtful, but enlargement of the testes has been reported in many subsequent articles. Spence (9) recently treated six patients with testosterone by injection, inunction, implantation of a tablet, and oral administration of methyl testosterone. All these methods were potent, the doses varying with the method and with the case. The best method has yet to be determined.

In testosterone there is no doubt that we have a potent androgen which will be of great value in the treatment of sexual hypofunction where response to gonadotropic treatment has not been obtained. Like all substitution treatments it has to be continued indefinitely. But in the boys at puberty who have responded to some extent to gonadotropic treatment it may be possible to bring them up to normal with testosterone and then omit it. The following is an account of a patient who has been under observation for some time.

CASE No. A4.—Plates No. 43 and 44. A young man of 23 years showed a small penis and scrotum and left testicle, while the right testicle was undescended. After four months' intensive treatment with Antuitrin S. the right testicle could be felt in the inguinal region, otherwise there was no change; 5 mg. of testosterone propionate daily for a month produced little further development, but daily injection of 5 mg. testosterone with Antuitrin S. 2 c.cm. produced a considerable change. In three months the penis enlarged a great deal, the scrotum developed, the left testis grew through to a lesser degree, while the right testis, although still very small, entered the scrotum. Pubic hair developed, and erections and emissions occurred. The voice took on a manly character but shaving was only necessary about once weekly. He felt more energetic during treatment, which is a usual experience. (An improvement in muscular strength with an increased resistance of the central nervous system against fatigue has been confirmed experimentally, during treatment with testosterone (10).) The dose of testosterone was very small in this case as it was limited by the expense, and probably a more speedy result would have been obtained with larger doses. In order to see how long the effect of the androgen lasted, treatment was omitted, in five months erections and emissions had ceased, shaving had been reduced to once a month, and the patient neither looked nor felt so well. Erections and emissions were immediately produced by an injection of 25 mg. of testosterone (neo-Hombreol), and subsequently he was satisfactorily maintained on a daily dose of 15 mg. of methyl testosterone by the mouth.

Primary Hypogonadism in Childhood

Hypogonadism in adolescence has been described and its course into adult life has been traced, now we will consider the earlier part of the natural history of the condition.

The history of emaciation and tall growth in childhood, which we obtained in a number of our adolescent patients, caused us to pay particular attention to thin children from the endocrine point of view, and the practice of routine measurement soon enabled us to pick out certain cases which appeared to fit into this category. The patients were brought to hospital, as a rule, because of severe and repeated "bilious attacks", or an ill-nourished appearance, and on examination were found to be tall for their age, the lower measurement exceeding the upper and the span the height. Evidence of defective genital structure was present in the boys, who constitute all our cases, as it is more difficult to make a certain diagnosis in little girls. We have followed some of these cases for years with apparent justification of the original diagnosis and will report two examples.

CASE No. 56.—Plate No. 40. A boy aged 9 years had always been thin and nervous. There were three normal siblings. At $5\frac{1}{2}$ years he had suffered from spasmodic torticollis, at 7 years bilious attacks started. The measurements were as follows:

Case No. 56	Age 9 Years	Age $12\frac{1}{2}$ Years	Age $13\frac{1}{2}$ Years
Head . . .	20.5 in.	20.5 in.	21.0 in.
Chest . . .	23.0 "	24.0 "	26.0 "
Abdomen . . .	23.0 "	24.5 "	27.5 "
Span . . .	56.5 "	62.0 "	66.0 "
Height . . .	55.5 "	62.5 "	66.5 "
Lower Measurement .	29.5 "	34.25 "	37.0 "
Upper Measurement .	26.0 "	28.25 "	29.5 "
Weight . . .	71.0 lb.	76.0 lb.	92.0 lb.

The height and span were above normal and the lower measurement already exceeded the upper by $3\frac{1}{2}$ in., although at the age of 9 years the upper measurement should still exceed the lower. The weight was above normal but he appeared thin because of his height. Very small testes were in the inguinal region. The teeth were crowded and irregular. Development of the epiphyses was normal and a stereo-radiograph of the skull showed a normal pituitary fossa. During the first year he was given energetic treatment consisting of Pregnyl 500 rat units weekly for four months, anterior pituitary powder for four months, Gonadotrophon (pituitary sex hormone from the anterior lobe itself) twice weekly for two months, and thyroid gr. $\frac{1}{2}$ B.D. for two months. During

the second year, a two-month course of Gonadotraphon was given, and later the same preparation was given daily for one month. During the third year a further intensive course of Gonadotraphon was given for one month. At the age of $11\frac{1}{2}$ years the B.M.R. was found to be -20 , so thyroid was re-started and pushed to larger doses, until he was taking gr. v B.D. without obvious result. The epiphyses were radiographed again at this stage ($11\frac{1}{2}$ years) and showed normal development. At the age of $12\frac{1}{2}$ years an improvement in general health and nervous symptoms and a cessation of bilious attacks resulted, the penis enlarged to normal, and the right testis could be pulled into the scrotum and had enlarged slightly, the left testis showing no change.

From the age of $12\frac{1}{2}$ to 13 years he had an intensive course of Pregnyl injections, and following this the scrotum developed, the testes enlarged to normal size, the penis became rather larger than normal, and pubic hair started to grow. Considering the large amount of treatment that he had had and the somewhat disproportionate development of the penis, it was thought advisable to stop treatment. Since then there has been no material change.

This patient is developing in the typical hypogonadal fashion; the measurements now, at the age of $13\frac{1}{2}$ years, show that the span and height have increased considerably, while the head has grown very little and he remains very thin. The difference between the upper and lower measurements has increased to 7.5 in., which is a remarkable figure. The epiphyseal development is normal. It is evident that treatment has had little effect except on the genital organs, and that, despite it, eunuchoid statural characteristics have developed. It is difficult, however, to account for these proportions, because the epiphyseal development has been normal throughout. This case appears to bear out the suggestion made before, that there is an excess of growth hormone in these hypogonadal cases. The low B.M.R. was an unexpected finding and contrasts also with the normal epiphyseal development. Efforts were made to increase weight by prescribing extra milk and haliverol with little success, but apart from thinness he looked well and no sign of any other physical complaint developed during the $4\frac{1}{2}$ years of observation.

CASE No. 81.—A boy aged 9 years. He had always been thin and puny and had suffered from bilious attacks. His father and eldest brother suffered from biliousness in the same way. The measurements were as shown in table on p. 184.

They show the usual characteristic features. The testes and penis were very small. The epiphyses were retarded, a stereoradiograph of the skull was normal. During the first year, when

Case No. 81	Age 9 Years	Normal for Age 9 Years	Age 14½ Years
Head	20·75 in.	20·9 in.	21·5 in.
Chest	22·5 "	24·6 "	25·5 "
Abdomen	21·0 "	22·3 "	25·5 "
Span	52·0 "	49·0-53·0 in.	63·0 "
Height	50·75 "	49·5-53·0 "	60·0 "
Lower Measurement .	26·5 "	24·0-26·3 "	32·25 "
Upper Measurement .	24·25 "	24·7-27·0 "	27·75 "
Weight	52·5 lb.	51·6-64·4 lb.	86·0 lb.

he was treated with posterior pituitary powder, the weight rose to 70 lb., bilious attacks almost ceased, and he appeared much improved. Since then he has been observed for four and a half years. Anterior and posterior pituitary powder was prescribed for nine months, anterior powder alone for thirty-three months, and thyroid gr. i B.D. for most of the time. At the start of observation the lower measurement exceeded the upper by 2·25 in., after five and a half years it exceeds it by 4·5 in., and like the previous case this gives an interesting confirmation of the significance of measurements taken as early as 9 years in indicating the type of individual which is going to develop, and another example in which treatment failed to prevent the development of disproportion, which, however, is not nearly so severe in this patient as in the last. Examination of the epiphyses at the age of 13 years showed that development was still retarded by one to two years. The B.M.R. tested at the same time showed an absolutely normal result, +1; there was therefore no indication for pushing thyroid therapy and the epiphyseal retardation was presumably due to hypogonadism. This does not appear unlikely at the age of 13 years, but is not so convincing an explanation of the same degree of retardation at the age of 9 years. Thyroid can play but little influence in this syndrome because growth is accelerated, not stunted, and the explanation must lie in an abnormal interplay of pituitary, gonadal, and possible adrenal influences. By the age of 14½ years the genital organs had enlarged to normal but there was no sign of secondary sexual characteristics. The epiphyseal development was retarded one year. He remained extremely thin and suffered from occasional bilious attacks.

These examples show the type of small child which may be expected to develop into the adolescent hypogonadal case. It forms an entity which may be picked out by the characteristic measurements and build, sexual under-development in

boys, and a history of nervousness and fat intolerance associated with "bilious attacks" or migraine. We have not made this diagnosis as yet in girls below the age of 14 years, although we know that it exists from the history of the adolescent cases. Both the boys and the girls probably form a section of that large group with fat intolerance which is termed "acidosis".

Prognosis, Diagnosis, and Treatment in Childhood

We have not had sufficient experience to state what the prognosis is in the untreated child, but from the histories of the older patients (e.g. Cases No. A1 and A2, pp. 174 and 175) it appears that many of them were tall and thin in childhood and evidently the endocrine disorder originated in prepubertal years. It is not suggested that all thin children fall into this group because the majority are due to some other organic disease, but it is important to remember that thinness as well as fatness may be a sign of endocrine disorder. If hypogonadism is suspected in early life, observation would determine whether normal development was taking place and treatment could be given at an age when some result might be expected. Confirmation of diagnosis may be obtained by the family history, the absence of signs of other organic disease, and the abnormal measurements.

Treatment has been devoted to efforts to improve nutrition by general means and to stimulate genital development. In the boys reported above (Cases No. 56 and 81), treatment was begun at an early age and persevered with for several years. At present we do not give them such energetic treatment at so early an age, but treat them on the lines suggested in Chapter 4, p. 93 *et seq.* We have not had enough experience to state how much benefit results from endocrine treatment in this group.

Possible Harmful Results of Gonadotropic Treatment

This is a convenient place to consider whether harmful results ever occur from the use of gonadotropic substances in young children. In an experience during ten years of the use of gonadotropic substances from pregnancy urine, from

the pituitary gland, and from mares' serum, and of crude pituitary extracts and pituitary powder intranasally, we have only had one untoward result. This was :

CASE NO. 82.—Plate No. 31. A boy of 8 years suffering from primary hypogonadism ; the right testis could not be felt, the left was minute and in the inguinal region. He was given the following treatment, Antuitrin S. 1 c.cm. three times weekly for four months, followed by Pregnyl 500 rat units weekly for four months, by which time the penis had enlarged, the left testis had become normal in size and was in the scrotum, the right testis could be felt in the inguinal region, the size of a pea. Treatment was omitted for one year and seven months, when one month's treatment with Pregnyl 500 rat units twice weekly was given. The penis was then noted to be large, the testes unchanged ; when seen three months later the condition was substantially the same. The patient now ceased attending and only reappeared in response to an enquiry fourteen months later, aged exactly 11 years. The mother stated that he had started to develop rapidly, shortly after his last attendance, and he showed a remarkable change. He had increased in all measurements, the span by 8 in., the height by $5\frac{1}{2}$ in., and the weight by no less than 20 lb. He had advanced in size from a boy of between 10 and 11 years to one between 13 and 14 years in the space of fourteen months. Instead of being rather a puny child, he was now remarkably muscular, the penis was larger than the organ of a full-grown male, the left testis was almost adult size, the right remained undescended, the general appearance, as will be seen from Plate No. 31, resembled very strongly a case of pubertas praecox. The epiphyseal development was slightly advanced. After this spurt, growth slackened and two and a half years later at the age of $13\frac{1}{2}$ years, the height had increased by $2\frac{1}{2}$ in. to $64\frac{1}{2}$ in., the span by $3\frac{3}{4}$ in., and the weight by 16 lb. to 123 lb. He was about the normal height for 16 years. The only further genital changes were that the right testis was now descended and of normal size for his age, while the left testis had enlarged to adult size. He experienced erections but stated that emissions were not present. The epiphyseal development was still slightly advanced for his age.

There is an interesting family history that both the father and the mother grew very fast after the age of 14 years, and the precocious development in this case may be due to treatment having stimulated an abnormal familial tendency, because the dose and duration of treatment were not excessive, nor did the effect arise immediately after treatment had ceased. There have been no mental changes and the condition is gradually passing

into normal development, without serious consequence. Besides this case 2 or 3 of our patients have developed a rather large penis.

We think that it is extremely important in all eunuchoid conditions to obtain normal genital development at about the normal age of puberty, not only for the direct effect on the patient, both mental and physical, but in the hope of preventing statural disproportion. These are strong arguments against waiting until the age of 15 or 16 years, as suggested by some authorities before treatment is begun. In order to obtain results some slight risk is justifiable. At present testosterone should not be given in prepubertal years.

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Imperfect Descent of the Testis

Failure in descent of the testis may be due to mechanical obstruction, to an inherent fault in the gland, rendering it incapable of reacting to the gonadotropic hormone of the pituitary, to an insufficiency of the gonadotropic hormone, or to a combination of these circumstances. Hence, as is borne out by experience, it is unlikely that any single therapeutic measure will be successful in effecting a cure in every case.

Descent of the testis from the abdomen is controlled by the pituitary gonadotropic hormone which is necessary for the growth of the interstitial tissue and the seminiferous tubules. During the 7th month of foetal life the testis passes along the inguinal canal to reach the external ring at the 8th month, and in the 9th month the scrotal position is reached (1). The normal passage of the testis may be

arrested at the internal abdominal ring or at any point along the normal line of descent owing to hormonal failure or to anatomical abnormalities. More rarely, the gland may take an abnormal path and be found in an ectopic position.

Cryptorchidism may be the only physical abnormality observed in the patient or it may be one of the physical signs found in endocrine syndromes such as have already been described. We are here discussing those cases in which imperfect descent is the only sign of disease. Bilateral abdominal cryptorchidism usually results in sterility because the spermatogenic tissue does not develop fully at the temperature inside the abdomen. It has been shown that a testis which is removed from the scrotum and placed in the abdomen undergoes degenerative changes which are similar to those found in individuals with cryptorchidism (2). Up to the age of puberty, retention of the testis is accompanied only by failure of development of the seminiferous tubules and interstitial tissue, but after this age atrophy occurs and increases with time (3). The internal secretory tissue of the imperfectly descended testis is not so severely damaged as the spermatogenic tissue, for secondary sexual characteristics may develop fully in cases of cryptorchidism.

Clinical Examination

When it has been established that imperfect descent of the testis is not part of an endocrine syndrome, particular attention is paid to the position of the gland in relation to the inguinal canal, its mobility, size, and consistency, the size and development of the penis and scrotum, and the presence or absence of hernia. In children, the cremasteric reflex is very brisk and contraction of the cremasteric muscle may draw the testis into the inguinal canal, especially if the weather is cold. To overcome this difficulty, the patient should be placed before a fire until he is thoroughly warmed, when full muscular relaxation is obtained.

Treatment

The purpose of all forms of treatment is to obtain full descent of the testis, combined with that degree of growth

and function which is normal for the age. The success which has been obtained by different methods is for various reasons difficult to estimate. We do not know how frequently the condition occurs because of the varying definitions of imperfect descent, and many published statistics have failed to differentiate cases of patients with imperfect descent from those in whom it is only part of an endocrine syndrome. The position is further complicated by the lack of general acceptance of a standard of cure ; a cure should mean the production of normality and not of testicular descent alone.

The treatment of imperfect descent of the testis may be (1) Expectant, (2) Surgical, (3) Hormonal.

Expectant Treatment

Spontaneous descent of the testis may eventually occur in more than half of the total number of cases from every cause (4) (5). For this reason and because of poor results obtained from surgical treatment, Johnson (5) advocates that endocrine treatment is unnecessary and that operation should only be performed when the patient is 16 years of age or more. In opposition to this view, Smith (6) urges that no untoward results are to be anticipated from delaying treatment until it has been ascertained that descent will not be normally accomplished at the age of puberty, but that surgical treatment should be carried out as soon as possible after puberty because atrophy of the germinal epithelium takes place after this age.

Surgical Treatment

In favour of the operation of orchidopexy is the knowledge that the scrotal position of the testis helps the maturation of the spermatozoa, and it is probable that the male gonad will produce more hormone in the scrotum than in a position where the temperature is higher, for it has been shown that transplantation of the testis or ovary into a rabbit's ear will cause maintenance of the glandular structure and production of testosterone (7). On the other hand, it is found that a successful scrotal fixation of the testis in cases

of cryptorchidism is not necessarily followed by hormonal adequacy and the development of spermatozoa, either from endocrine or mechanical reasons.

Hormonal Treatment

The substance used in hormonal therapy is chorionic gonadotropin (prolan), which is obtained from pregnancy urine. Gonadotropin acts in the same way as the gonadotropic hormone of the pituitary, causing descent of the testis, stimulation of the interstitial tissues, and promotion of the appearance of the secondary sexual characteristics. It is preferable to use gonadotropin of human origin, e.g. "Pregnyl", which does not cause the formation of inhibitory substances which prevent continued treatment (8). Our personal observation confirms the experience of others (9) that testicular degeneration does not occur with therapeutic dosage of gonadotropin derived from human pregnancy urine.

The degree of success which may be expected in the hormone treatment of large numbers of cases is about 60 per cent (10) (11) (12). This figure includes cases of imperfect descent from all causes. We and others (12) have observed that the most satisfactory results are obtained when imperfect descent of the testes is accompanied by evidence of endocrine imbalance and when the treatment is begun before puberty.

When failure of testicular descent is one of the signs of an endocrine disorder, it should be treated according to the methods indicated under the headings of the particular disease. If other endocrine signs are not present, treatment should be begun with gonadotropin, preferably at about 10 years of age, giving 300 to 500 rat units intramuscularly up to a total dosage of 10,000 units. If the response is minimal, treatment is omitted for two months and then a further course of gonadotropin is administered. It is found that the testis develops and descends rapidly if it is capable of response to hormone treatment and if it is not retained by anatomical abnormalities. A greater increase of dosage and prolongation of hormonal treatment does not yield

satisfactory results. If hormone therapy is not followed by adequate improvement, surgical treatment should be considered at once, bearing in mind that any increase in the development of the testis and cord which has been produced materially improves the chances of a successful operation. Further improvement may be derived by administering gonadotropin after orchidopexy. Zelson and Steinitz (13) have successfully treated cases of imperfect descent by injecting small amounts of male sex hormone. They also report (14) that, by combined injection of testosterone propionate and gonadotropin, complete descent has been obtained in the cases of boys who had previously been treated with either hormone alone or successively without any effect. We have not, up to the present, used testosterone under the age of puberty.

Complications of Treatment

A hernia may develop during the course of treatment (9). Excessive treatment may lead to over-development for the age and premature epiphyseal closure. The occurrence of itching of the genital area, priapism, or frequent emissions are a warning that dosage has been too vigorous and such events are particularly to be avoided in children, who may develop an abnormal sex consciousness. In some instances the testis may not be capable of response and prolonged treatment may lead only to overgrowth of the penis. Precocious hypertrophy of the prostate, with consequent interference with urination, has been recorded following lengthy hormone treatment (15). From our experience, the danger of over-dosage is negligible if treatment is confined to two courses of gonadotropin as described above.

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Treatment of Acne Vulgaris

This is an appropriate place for a note on the treatment of this condition, because acne is an invariable accompaniment of primary hypogonadism from the age of puberty, and is often found in both sexes in many other varieties of endocrine imbalance, particularly where gonadal function is deficient. It must be understood that we do not state that acne is invariably associated with endocrine disorder ; we say that endocrine disorder, particularly hypogonadism in adolescents of both sexes, is often accompanied by acne. Stokes (1) has recently reviewed the whole problem of acne in a comprehensive manner, pointing out the great variety of factors involved. Acne is a very common disorder, and many cases occur in patients in whom no evidence of endocrine disorder can be found. We have not treated these unselected patients and cannot express an opinion about them, but the published results of endocrine treatment are not definite. We can express an opinion about those patients in whom there is endocrine imbalance ; the appropriate endocrine treatment, usually one of the gonadotropic preparations, almost always cures the acne very quickly, even if it is of many years' standing. We have seen dramatic results in a sufficient number to exclude the possibility of coincidence.

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CHAPTER 9

PROGERIA : SIMMONDS'S DISEASE : VON BERGMANN'S PITUITARY EMACIATION : ANOREXIA NERVOSA

Progeria (Premature Old Age)

IN this rare condition an arrest of growth is followed by the development of senile change leading to premature death although the patient still shows an infantile stature and sexual development. It was described by Sir J. Hutchinson (1) in 1886, but in 1897 Hastings Gilford (2) gave the first detailed account and suggested the term progeria. In one of his cases the condition started at the age of 6 months, when the hair began to fall out and the nails to shrivel. At the age of 15 years he was like "a wizened and dwarfish old man", only 45 in. high and weighing 35 lb. The absence of superficial fat, the scanty grey hair on the scalp, the dry skin, weak muscles, piping voice, and large knuckles of the hands presented a striking picture of old age. At the same time childish and infantile features were present, for the anterior fontanelle was not closed, many milk teeth were present among some of the permanent set, the genital organs were slightly small for his age, and pubic hair was absent. This curious mixture of youth and old age is characteristic of the condition, and Hastings Gilford points out that the same thing was observed in the internal organs after death, for autopsy at the age of 18 years showed an enlarged fibrous thymus gland and extensive atheroma of the mitral and aortic valves with marked coronary sclerosis. The thyroid was normal, the kidneys fibrous, the adrenal glands shrivelled, and the stomach and intestines so atrophied as to be almost transparent. The pituitary was normal to the naked eye but

was not examined further. Ossification of the epiphyses was slightly advanced.

Atkinson (3) has collected 14 cases from the literature which he thinks are entitled to this diagnosis and they closely resemble the one which has just been described. Exchaquet (4) reports a typical case in a girl of 14 years who showed some additional points of interest. Decalcification of the bones was extreme and the production of several sets of teeth was a strange anomaly, as one would expect that to be associated with signs of hyperpituitarism. The first dentition was replaced by a second, and this by a third, and even by a fourth, and the mother said that the teeth fell out and grew again at once. The upper middle incisors were three or four times larger than the other teeth, which were the usual size. The patient had a huge appetite and the skin felt very hot, corresponding to a B.M.R. of +58 to +69. The author concludes that the condition is due to a dissociation of pituitary functions, a defect of growth hormone with an excess of thyrotropic and parathyrotropic hormones.

Simmonds's Disease

(*Synonyms* : Simmonds's cachexia or syndrome, pituitary cachexia, multiple ductless glandular sclerosis—Falta)

In 1914 Simmonds (5) described a clinical syndrome which has since been associated with his name. It is due to a destruction of the anterior lobe of the pituitary gland by various causes, for example, new growth or tubercle, or most frequently, ischaemic necrosis following childbirth, especially when severe haemorrhage has taken place. Secondary atrophic changes take place in the other endocrine glands, so that a syndrome is produced which suggests hypofunction of the pituitary and thyroid, together with an asthenic condition resembling Addison's disease and signs of premature senility. Calder (6) in a review of 70 cases predominantly female confirms the constancy of the destruction of the anterior lobe of the pituitary gland

and the atrophic changes in the other endocrine glands. He presents the following conclusions: "Emaciation develops sooner or later and is a striking and characteristic feature. Falling of the teeth and hair, particularly that of the axillary and pubic regions, trophic changes in the nails and thickening and loss of lustre of the skin combine to give the patient the appearance of premature senility. General muscular weakness is accompanied by corresponding atony of the gastro-intestinal tract with marked constipation, vomiting and a consequent distaste for food. There may be a sub-normal temperature, with a subjective feeling of chilliness. In those cases in which the basal metabolism has been measured it was subnormal; the blood-pressure was invariably low. In women menstruation ceases and sterility ensues, and in men there results sexual weakness which may amount to complete impotence. Many patients display peculiar forms of pathological sleep; coma frequently precedes death." This syndrome is very rare in childhood but a number of cases have been reported in adolescence. Dunn (7) describes a characteristic example in a girl who at the age of 12 years began to suffer from headache, anorexia, coldness of the hands and feet, and polydipsia followed by cessation of menstruation and rapid loss of weight. Some months later the breasts were noticed to be getting smaller, the skin became dry, the hair started to fall out, and she became very depressed. By the time she was 13 years old symptoms had progressed, the facial expression was aged, the skin was thickened, the blood-pressure was 70-90 mm. Hg. systolic, and the external and internal generative organs were judged to be atrophic. Radiographs of the skull were normal and the epiphyses showed normal development. The height was 64.75 in. and the weight 85 lb., a loss of 58 lb. The Wasserman test and all other laboratory tests gave normal results, the B.M.R. being - 3. No evidence of tuberculosis could be found and the Mantoux test was negative in forty-eight hours. The diagnosis of Simmonds's disease was made on the acute onset of illness with rapid loss of weight in a previously healthy child, the sudden cessation of menstruation after normal menses for

a year, the genital atrophy, and the absence of any evidence of other disease. She was treated with injections of Armour's anterior pituitary liquid, and later with Progynon B in addition, in large doses, with a return to normal in every respect. The internal generative organs enlarged, menstruation returned, the normal body contours were re-established with enlargement of the breasts, and subjective symptoms disappeared. Similar results have been reported in other cases usually with some preparation of pituitary gland, although the great majority of cases end fatally. Thyroid gland is quite ineffective in treatment. The reason that most of the cases have occurred in the female appears to be due to the fact that childbirth is the most important single aetiological factor, but the following case shows that the same syndrome may occur in males, when pituitary function is depressed. Plummer (8) and Jaeger describe a case in a young man of 22 years. He developed symptoms of polydipsia, fatigue and anorexia, the testes atrophied and the hair began to fall. He improved for a month with treatment by daily injections of 200 rat units of pregnancy urine gonadotropic substance, but later sank and died. This treatment would only stimulate testicular secretion and would have no effect on the other ductless glands, so that it is not surprising that the effect was limited. A glioblastoma multiforme was observed *post mortem* in structures adjacent to the pituitary gland and exerting pressure upon it. In section the pituitary gland showed oedema and its normal architecture could not be made out, so that presumably a functional disturbance of the gland had been produced. In Simmonds's disease a tumour or other gross change has often been demonstrated, but the occurrence of cases which recover suggests that functional disturbance of the gland is the underlying cause in those instances. The diagnosis of Simmonds's disease is only unequivocal in very well-marked examples and some would restrict the term to those cases confirmed by autopsy, but by analogy with other endocrine disorders we should expect to find many partial examples of the syndrome for one fully developed case, and that is the consensus of opinion in recent litera-

ture (19). The chief interest in the condition as far as this book is concerned is to point out the resemblance to other syndromes of pituitary failure, of which it affords so acute an example.

Von Bergmann's Pituitary Emaciation

Von Bergmann (9) described a condition occurring usually in females at puberty, during adolescence, or following pregnancy, characterised by emaciation, fatigue, anorexia, and amenorrhoea. In the adolescent retarded sexual development is found, and in all cases there is hypotension, a low B.M.R., low blood-sugar, and an increased sensitivity to insulin. Kunstadter (10) reported two cases recently, one of which had the following history :

The childhood was normal but at the age of $15\frac{1}{2}$ years the weight dropped from 105 to 60 lb. In three months she developed anorexia and vague abdominal symptoms. During the next three and a half years she spent varying periods in hospital, gaining weight temporarily but never exceeding 85 lb. All investigations were negative. Menstruation occurred for the first time at the age of $16\frac{1}{2}$ years. Eighteen months later the height was 63 in. and the weight 81 lb. The breasts were undeveloped, pubic hair was sparse, the clitoris was hypertrophied, the introitus undeveloped, the uterus very small, and the ovaries impalpable, and only two further scanty periods had been experienced. Considerable improvement occurred after treatment with pituitary gonadotropic hormone and oestrogenic substance. Menstruation became established at 19 years old and was regular at the age of 20 years.

The chief point of interest in the description of this syndrome is that we can see no difference at all between these cases occurring in childhood and adolescence and those described under Engelbach's term—non-adipose primary hypogonadism (*q.v.*), and we regard the two conditions as identical. The resemblance to Simmonds's disease is also quite obvious, although the condition is more chronic and with a more favourable outlook.

Anorexia Nervosa

The description of the last two syndromes and non-adipose hypogonadism is in many ways very suggestive of anorexia nervosa, and although the latter syndrome is of psychological origin, it is interesting to consider it in relation to these conditions. Anorexia nervosa is characterised by complete loss of appetite and refusal of food, with the resulting effects of starvation, and is most common in the female sex from the age of 15 to 25 years. The essential feature is the refusal of food, and as the patient accustoms herself to taking less and less, the appetite diminishes, the condition becoming a vicious circle so that death from emaciation may ensue. The condition starts insidiously; amenorrhoea may precede the other symptoms, and even when emaciation has become extreme the patient often remains active mentally and physically. An emotional difficulty always lies behind the symptoms, often of a sexual nature and not infrequently involving the mother. It is usually imperfectly understood by the patient, and some superficial reason may be given for refusing food, such as "slimming" on account of real or supposed obesity. Ryle (11) has recently given a full description of the syndrome and from a large experience stresses the psychological origin of the trouble. The treatment consists of isolation and feeding in an institution, and with firm handling recovery usually follows. An effort should be made to determine the nature of the conflict behind the symptoms, so that if possible it can either be resolved or the patient brought to see it in a new light.

Refusal of food arises of course from many motives and may be a symptom of a grave psychosis, such as schizophrenia or manic-depressive insanity. These conditions are not included under the term anorexia nervosa, for the latter resembles rather mono-symptomatic hysteria of the conversion type with paralysis of arm or leg, although, as Nicolle (12) has pointed out, it differs from hysteria in a number of important ways, such as the fact that the patient does not seek sympathy and attention. Although anorexia

nervosa is due to psychological causes and its pathology is largely the pathology of starvation, yet that does not mean that there are no other factors which enter into it.

Amenorrhoea is a constant symptom and has been attributed to the effects of starvation. When, as not infrequently happens, it precedes the other symptoms by a number of months, it is thought to be due to the original mental stress which initiates the syndrome. But it is to be noted that it is usually the last symptom to clear up and may persist for some time after the patient has returned to normal health in other respects. Sheldon (13) has carefully examined the records of physical constitution of the cases in the literature. Two patients reported by himself were below 5 ft. in height, and there are several other cases in the literature noted as being small. There is abundant evidence that many of the female patients are sexually underdeveloped. Sheldon (13) reports a case of a woman aged 35 years who had suffered from anorexia nervosa for many years; pubic hair was scanty and dysmenorrhoea so severe that hysterectomy was finally performed and an infantile uterus was then found. We would place this case in the group of primary non-adipose hypogonadism. Sheldon concludes that in a number of cases "there is significant delay—or weakness—in the sexual development of puberty". Another fact needing explanation is the fine downy hairs which often appears on the face, arms, and trunk, sometimes with coarser hairs on the chin. Again we would mention that a similar condition is found in primary hypogonadism. Recently we saw a girl of 17 years suffering from this condition whose chief complaint was of a downy growth on the upper lip. Perhaps it is a sign of alteration in the normal androgen-oestrogen ratio in these cases, and this suggestion is rather supported by the finding of Birley (14), who notes that female cases show a tendency towards a male distribution of pubic hair, while the reverse may be found in males.

There are a number of instances in which anorexia has developed in an effort to combat adolescent plumpness, but some of the cases suggest that the term obesity might well

be applied to them and furnish another indication of the possibility of pituitary dysfunction. Sir W. Langdon Brown (15), in an interesting letter to the *Lancet*, corroborates from his own experience that anorexia nervosa is often preceded by obesity, and notes that the subjects are often feminine Peter Pans who are afraid of growing up, and that the close association between the emotional centres in the diencephalon and the pituitary gland furnish an explanation of how the emotional state may inhibit pituitary function. The Peter Pan attitude is of course the typical eunuchoid mental state as we have stressed before. The B.M.R. is low in these patients as it is in Simmonds's cachexia, and furnishes another point of resemblance to the condition. A flat type of blood-sugar curve has been reported in anorexia nervosa as in hypopituitary conditions, in which a minimal rise takes place after the injection of 50 g. of glucose, but Ross (16) has investigated the carbohydrate mechanism and considers that these curves are the result of inanition and cannot be considered evidence of pituitary dysfunction. Ross strongly agrees with Ryle in attributing the condition to psychological causes and in stressing that the subsequent state of inanition is sufficient to account for any abnormal physiological findings. Sheldon's view is that, in the cases occurring between the ages of 15 and 25 years, the evidence of pituitary dysfunction is such that we are really dealing with a "functional" Simmonds's disease. Grace Nicolle (17) has contributed a thoughtful review of the subject. After recognising the resemblance of anorexia nervosa to Simmonds's disease, she points out certain important differences—the onset of Simmonds's disease is abrupt, that of anorexia nervosa is insidious; in the former loss of weight precedes the reduction of food, in anorexia nervosa it is the result of starvation. Simmonds's disease is confined to females and often occurs in circumstances such as childbirth, which might induce pituitary exhaustion, and the premature ageing of Simmonds's disease is not seen in anorexia nervosa. For these and other reasons Miss Nicolle does not attribute anorexia nervosa to pituitary dysfunction but to primary ovarian failure, the interrelationships of these glands

allowing many variations in the picture.

It is interesting to comment on these varying views. In the first place, the immediate psychological origin of the trouble due to emotional stress cannot be doubted, for we know from the subsequent history of some of the cases that complete recovery followed by a normal life may take place. The patient, who probably has a psychopathic constitution, refuses food for a mental reason, and starvation follows with its physical accompaniments. Now, does this constitute a complete explanation? In some cases doubtless it does; in others, this explanation does not suffice.

We have described in Chapter 8 a condition termed primary non-adipose hypogonadism characterised by an insidious onset and prolonged course, loss of weight or even emaciation, nervous symptoms, hirsuties, sexual under-development, amenorrhoea, and absence of signs of premature ageing, which appears to us to give an exact picture of the physical constitution of the well-marked case of anorexia nervosa. Primary hypogonadism occurs in both sexes, as does anorexia nervosa. If the history of Case No. A1 (p. 174) is read again it will be seen that this patient corresponds in all physical characters to the above description. If an emotional stress had at any time been added to the picture, she could very easily have become a typical case of anorexia nervosa. We have already pointed out that Sheldon describes an obvious case of hypogonadism as an example of anorexia nervosa, and we have little doubt that primary hypogonadism is the endocrine syndrome which underlies the physical constitution of many of those cases of anorexia nervosa who show sexual under-development. Primary hypogonadism is found, like all other endocrine syndromes, in varying degree, and search should be made in all cases of anorexia nervosa for evidence of its presence. It is due to the absence of gonadal hormones, so that an explanation of both the male and female cases is found. As has been stated above (p. 166), it is by no means certain whether this defect should be regarded as primary, or as secondary to a pituitary defect, but it is convenient to regard it for the present as a primary gonadal syndrome,

for it differs in several respects from other examples of sexual under-development due to pituitary dysfunction. The interrelationships of the pituitary and the gonads are so intimate and complex that it is almost impossible to determine clinically where the influence of either starts or ends, but anorexia nervosa cases correspond more closely to those described under primary hypogonadism than under Simmonds's cachexia. If evidence of hypogonadism is found in a case of anorexia nervosa, then energetic endocrine treatment as described in Chapter 8 should be given.

The Relation of the above Syndromes to one another and to other Endocrine Disorders

Anorexia nervosa has already been discussed in this connection, but interesting points arise among the other syndromes. Simmonds's disease, progeria, and anterior lobe hypopituitarism (growth defect) show close resemblance in some respects and form a series varying from chronic to more acute change. The patient with retarded growth development due to anterior hypopituitarism develops slowly with poor muscular development, remains sexually infantile, the skin becomes wrinkled, the hair drops out, and long before the normal time the picture of age is presented (Plate No. 25). Simmonds's disease is a somewhat quicker process; an abrupt onset is followed by loss of weight, reduction in size of the internal organs, diminution of the primary and secondary sexual characters, and a wrinkling of the skin and loss of hair again lead to an aged appearance. Progeria is an even more astonishing condition in which in early life growth stops, the hair drops out, the subcutaneous tissue disappears, the skin becomes wrinkled, and while still of youthful age and infantile sexual development, the patient dies showing senile change. This syndrome is even more dramatic in its effects than Simmonds's disease, though bearing an obvious relation to it. Those three syndromes are all due to anterior pituitary failure, the different effects presumably being due to the varying degree of failure of the gland. But, as we have stated so frequently, the number of dissociations of pituitary function appears

infinite. For example, Exchaquet's case of progeria, quoted above, showed typical stunting of growth, wasting, loss of hair, and appearance of extreme age in a girl of 14 years. Nevertheless evidence of hyperpituitary function was present in respect of the thyrotropic hormone, for the B.M.R. was + 63, and the parathyrotropic hormone was probably also in excess, for the calcium of the bones was much diminished. This suggestion is supported by the unexpected finding that the child had already produced three or four sets of teeth. Primary hypogonadism was discussed in relation to anorexia nervosa and has also an obvious relation to Simmonds's disease and progeria, although not of so close a nature, for the growth hormone of the pituitary is normal and, perhaps for that reason, the patients do not develop an aged appearance. Von Bergmann's pituitary emaciation does not need separate discussion because we consider it identical with primary hypogonadism. The question of what symptoms are due to primary pituitary defect and what are due to gonadal hormone defect is bound up with these syndromes, and at present no clear answer can be given. Many cases of Simmonds's cachexia have been reported in which autopsy revealed gross damage to the anterior pituitary lobe, but de Gennes, Delarne, and Rogé (18) describe a typical case in which no gross or microscopic change in the pituitary was found, but the ovaries and suprarenal cortex showed complete atrophy with some alteration of thyroid structure. Such findings emphasise the close relationship between these syndromes but leave the exact explanation at present beyond our grasp.

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CHAPTER 10

ENDOCRINE DISEASE OF THE THYROID GLAND

THERE are two main divisions of disease of the thyroid gland: (1) due to partial or complete failure of function, (2) due to excess of function. In the first group, which is the one most commonly encountered in childhood and adolescence, the clinical characteristics vary greatly with the age at which lack of function has produced its effects. These manifestations of hypothyroidism will be described under the headings of (1) Congenital Hypothyroidism, (2) Juvenile Myxoedema, (3) Atoxic Goitre.

Congenital Hypothyroidism

Two types of congenital hypothyroidism are encountered, the sporadic and the endemic, both of which lead to the development of the same mental and physical characteristics.

Apart from changes in the thyroid gland, the morbid anatomy of the two types is the same. The bones are short because of delay in growth and the epiphyseal cartilages show delayed ossification. The thymus often persists and the pituitary gland may be enlarged. Myxoedematous changes are present in the skin, subcutaneous tissues, and mucous membranes.

Sporadic cretinism, the type which is most frequently found in this country, is caused by a failure of development or an atrophy of the thyroid gland (1). Sometimes, in compensation for the non-development in the usual situation, active glandular tissue is present either at the beginning of the thyroglossal duct at the base of the tongue or along its course, in which case the development of a myxoedematous condition occurs when the tissue is no longer

functionally adequate. Sporadic cretins are usually the children of normal parents.

Endemic cretinism occurs in the regions where there is a relative deficiency of iodine and where, in consequence, many people are goitrous. The cretin itself usually does not have a large goitre but the gland does not contain sufficient active secretory cells. The pre-natal history of such a patient is of considerable value. The mother may be goitrous or have suffered during this or previous pregnancies from symptoms caused by a lack of thyroxin. Repeated abortions may have occurred, other pregnancies may have been terminated by still-births of over-weight infants, or other children in the family may show evidence of mental deficiency. It may happen that the mother has put on excessive weight during pregnancy and has failed to return to normal after parturition. Sometimes a large increase of weight is accompanied by albuminuria and mental sluggishness due to the occurrence of myxoedema, the effects of which disappear after childbirth.

Clinical Features

In early months the infant may be little different from normal apart from general backwardness in growth and slowness in reaching the stages marking development in mentality. It is possible that some thyroid hormone passes through the placenta or is made available by the breast milk, thus delaying the onset of the symptoms (2). Breast feeding is, however, difficult because of the large tongue and flabby lips, and digestive disturbances are common, so that the child, which is frequently over-weight at birth, may become thin from malnutrition.

When the full effects of the lack of thyroxin are present, the clinical picture is not difficult to recognise (see Plate No. 47). The height is much less than normal for the age, for the lack of skeletal growth is particularly evident in the long bones and leads to persistence of the infantile type of dwarfism in which the upper measurement is longer than the lower. Radiographic examination is extremely helpful in the diagnosis of the cause of this dwarfism, for in hypothy-

roidism there is always delay in the appearance of the ossific centres owing to the slowing-up of the metabolic processes : in old-standing cases, the bones may show an increased density owing to the defective mobilisation of calcium : the epiphyses may also have a stippled appearance due to irregularly situated patches of ossification (3), and in untreated cases they may remain permanently open. The skin of the cretin is slightly yellow, cool, dry, and rough and may be covered with a soft down. Both skin and subcutaneous tissues are thick and pads of fat are present above the clavicles in older children, though they are less common in infants. The cretinoid facies is distinctive. The face is broad, the bridge of the nose depressed, the nostrils flared out, and the heavy lidded eyes are set wide apart. The lips are thick and frequently remain open to allow of the protrusion of the over-sized tongue. The voice is low-pitched and hoarse because the mucous membranes share in the general thickening due to myxoedematous infiltration ; this infiltration, together with the hyperplastic lymphoid tissue of the naso-pharynx and the enlargement of the tongue, combines to prevent normal respiration through the naso-pharynx and causes difficulty in feeding. The hair is coarse, dry, and scanty, and palpation of the skull shows that there is much delay in the closure of the fontanelles. The first dentition appears late, the teeth erupt in irregular order and readily become carious. When the second dentition appears, the irregularity of eruption may allow those that have appeared to grow to full size, thus crowding the later arrivals out of position. It sometimes happens that the lateral incisors are small or fail to erupt. Movements of the face and limbs are slow and muscular weakness is responsible for a protuberant abdomen and the frequent presence of an umbilical hernia. The sex organs are hypoplastic at birth and in severe cases fail to show any development, so that puberty is indefinitely delayed. Growth of the intelligence is as backward as somatic growth ; clean habits may not be acquired for years and the ability to walk is correspondingly delayed. Speech is limited to a few words and the general mentality at adult age may be

no more than that of a child of 5 years of age; many cretins are deaf and dumb. These changes in mentality are probably referable to failure in cerebral development or to changes in cerebral structure caused by lack of thyroid hormone during late foetal life (4) (33) (34).

The blood-count shows a secondary anaemia of the hypochromic type. The blood cholesterol may rise to 700 mg. per 100 c.cm. but a normal level does not rule out hypothyroidism if no thyroid treatment has been given (32). The blood iodine may be reduced from the normal 12 grammes per 100 c.cm. to 5 grammes per 100 c.cm. (5). The serum phosphatase measurement is a reliable index of thyroid deficiency in childhood. It is found to be abnormally low (less than 4.5 Bodansky units) in hypothyroid children who have not received thyroid treatment (32). A glucose tolerance test shows a flat curve, indicating an increase of tolerance. The urine shows no spontaneous creatinuria as in normal people (6) and the administration of creatine does not cause its excretion, as myxoedematous persons have an extreme tolerance for creatine. The administration of thyroid gland to cases of myxoedema causes excretion of creatinine (7). A mild albuminuria is not uncommon in myxoedematous conditions.

The body temperature remains subnormal, rising little even with infections, and the pulse rate falls in conformity with the slowing-up of the metabolic processes, as is observed in estimating the basal metabolic rate (8). In those patients who are able to co-operate, the estimation of the basal metabolic rate is an invaluable procedure and shows a lowering of as much as 40 per cent in severe cases. In most cases, however, considerable difficulty is experienced in obtaining metabolic estimations in these children, and it is more satisfactory to estimate thyroid deficiency by the delay in the appearance of the centres of ossification (9). Cretins are uncomfortable in cold weather because their metabolism is sluggish and the muscle tonus low; the same defects are responsible for their obstinate constipation.

Although cretinism may result either from a failure of thyroid development or from inadequacy of functioning

thyroid tissue in a fibrotic gland, the effects are the same. The pituitary gland is sometimes enlarged, possibly in an effort to provide thyrotropic hormone to stimulate thyroid function, and the thymus participates in a general hyperplasia of lymphoid tissue. It is not clear why the genitalia and the secondary sexual characteristics do not develop fully. These effects may be produced by the general lowering of metabolism, slowness of growth, and possibly slowness of differentiation of the tissues following lack of thyroid hormone, or may be due to pathological changes induced in the anterior lobe of the pituitary gland.

Minor degrees of hypothyroidism are by no means uncommon, and it is of the utmost importance that the condition should be recognised in the early months before it is too late to bring the child back to normal. The following case well illustrates the process of events that may occur.

CASE No. 144.—Plates No. 45 and 46. Female child aged 1 year 7 months.

Past history.—Birth weight, $7\frac{1}{2}$ lb. She then gained 6 oz. a week until 9 months old, when she was 22 lb. At 9 months she had influenza and whooping-cough, and after that grew very slowly. She sat up with an effort at 10 months and stood at 14 months, but did not walk until after treatment had been instituted for about five months (when 2 years old). The mental level was noticed to be deficient at 12 months. When brought up for examination the main complaints were mental dullness, constipation, restless sleep, and slow growth.

Clinical features.—The patient had a cretinoid facies (see Plate No. 45) with a sallow dry skin. She was rather fat and had pads above the clavicles; a large tongue was present and she had only cut two upper and two lower central incisors. An umbilical hernia was present and the rectum prolapsed. The child stood up but was lethargic and took little interest in her surroundings. The anterior fontanelle was open. Investigations showed retarded epiphyseal development, the os magnum and cuneiform bones being much under-developed. The Sigma reaction of the mother was negative.

The patient was given thyroid (fresh) gr. i B.D., and during the first month there was a noticeable improvement, for she became less lethargic, had a better appetite, and cut three teeth, which were followed by the appearance of five more in the next month. In three months the tongue was of normal size. In

five months she was walking, and steady improvement has continued. The anterior fontanelle closed at $2\frac{1}{2}$ years, and at this time she could say a good many words. At 3 years 3 months she spoke quite well but did not ask questions, and the epiphyseal development had advanced to normal. The thyroid dosage was gradually increased to gr. v a day.

At 4 years 3 months the psychologist gave the following report: "Chronological age: 4 years 3 months; Mental age: 4 years 1 month, I.Q. 96".

The measurements given below show the rapid physical development:

Case No. 144	Age $1\frac{1}{2}$ Years	Age $2\frac{1}{2}$ Years	Age 3 Years	Age $4\frac{1}{2}$ Years
Weight .	Not taken	Not taken	30.5 lb.	38.0 lb.
Head .	19.5 in.	20.5 in.	20.75 in.	21.0 in.
Chest .	19.0 "	20.0 "	20.0 "	21.0 "
Abdomen	19.0 "	18.5 "	16.5 "	21.5 "
Span .	27.0 "	34.0 "	35.0 "	40.0 "
Height .	29.5 "	33.5 "	35.0 "	39.0 "
L.M. .	12.5 "	15.0 "	15.0 "	18.0 "
U.M. .	17.0 "	18.5 "	20.0 "	21.0 "

This case shows very well the response to treatment in mild hypothyroidism, which in this instance was probably aggravated by the severe illness at 9 months.

Diagnosis

Provided that excessive stature in the parents, prolonged gestation or maternal diabetes can be excluded, a weight of over 9 lb. at birth should arouse suspicion that there is thyroid deficiency, more particularly if the mother has become obese during the pregnancy.

Cretinism must be differentiated from rickets, mongolism, achondroplasia, and other forms of infantilism. The pot-belly, delay in closure of the fontanelles, and muscular weakness of the rickety child bear a superficial resemblance to cretinism, but the bossed skull, enlargement at the costochondral and epiphyseal junctions, the preservation of the normal statural relationships and the normal mentality should make the diagnosis simple, though it should not be forgotten that rickets and cretinism may both make their appearance together at the age of weaning. Mongolism is

unlike cretinism in being present at birth, and although the facial appearance and mental defect bear a fleeting resemblance to cretinism, it will be noticed that the head is small and rendered short by a flatness in the occipital region, and the palpebral fissures, though narrow, slope upwards and laterally and that the tongue is large and fissured; moreover, the skin is smooth and fine, dwarfism is uncommon, and there is no delay in the appearance of the ossific centres (10). Achondroplasia is a congenital condition in which there is dwarfism due to an abnormal shortness of the humerus and femur, accompanied by a prominence of the forehead and depression of the bridge of the nose which are caused by a synostosis *in utero* of the two parts of the sphenoid and the sphenoidal process of the occipital bone. The children are mentally alert and there is no delay in ossification (11). The mental dullness, dwarfism, and depressed bridge of the nose of the congenital syphilitic are features also present in cretinism, but here a routine Wasserman reaction will make the diagnosis obvious. Hypertelorism (12), which is caused by a developmental error of the sphenoid bone, may also resemble cretinism because of the wide-set eyes, flattened bridge of the nose, and frequent mental dullness, but the other characteristics of cretinism are not present.

The final proof of a hypothyroid condition is given by the rapid response to thyroid medication. Difficulty may arise if thyroid gland has already been administered, thereby masking the symptoms; in this case a temporary cessation of treatment will soon reveal the true nature of the disease.

Treatment

In some cases where hypothyroidism has been detected in other children of the family it should be possible to anticipate the condition and, by giving the mother an adequate amount of thyroid gland during the pregnancy, to prevent the development of the disease in the child.

The most favourable effects of substitution therapy are to be expected in patients who have begun treatment in the first few months of life. Some mental retardation is likely

to persist if therapy is delayed until 3 or 4 years of age, even though physical development is within the normal limits for the age. Once the disease is diagnosed, treatment must be continued uninterruptedly for an indefinite period, increasing the dosage according to the individual requirements. As a general rule, it is possible to begin by giving $\frac{1}{2}$ grain of desiccated thyroid gland daily or 2 grains of the fresh gland by mouth without producing symptoms of hyperthyroidism; it is seldom necessary subsequently to exceed a daily dosage of 3 grains of desiccated gland. The same dose should be continued for about three weeks (13), because the action of the hormone is not fully evident at once. As individual needs vary, it is necessary to push the dosage to the limits of tolerance and then to reduce the amount by one-third for subsequent dosage. Excess of thyroid gland produces at first fretfulness, irritability, and an unusual activity; the more toxic effects are colic, diarrhoea, loss of weight, and a rise in the pulse rate and temperature.

As thyroid treatment takes effect, the cretinoid facies disappears and the weight becomes normal for the height. Progress in growth and development should be maintained at a more rapid rate than is usual for the age, in order to bring the child within normal limits. The improvement is most satisfactorily estimated by comparing the body measurements and osseous development with the normal for the chronological age, and this should be done at intervals of three months for the first year of treatment. An estimation of the mental age can be made at yearly intervals. Wilkins (14) believes that the most rapid improvement and best end results are probably to be obtained by giving sufficient thyroid gland to produce a very slight degree of hyperthyroidism, while taking care not to cause toxic symptoms. As a further indication of improvement, it will be observed that the blood cholesterol decreases to normal; the basal metabolic rate can be shown to rise if the child is able to co-operate.

If treatment with thyroid gland does not bring about satisfactory improvement, the possibility of involvement of the pituitary gland must be considered. If the proportions

remain infantile or growth is much delayed, injections of growth hormone should be given, and at a later stage the secondary gonadal defect should be treated with gonadotropic hormones, bearing in mind, however, that the resulting gonadal activity will slow up growth and cause the epiphyses to join.

Thyro-pituitarism

This is a congenital hypothyroidism which has been complicated in early childhood by pituitary gland failure, and is fully described in Chapter 4. p. 98.

Juvenile Myxoedema

Juvenile myxoedema is a condition due to a chronic acquired deficiency of the thyroid hormone. It may be brought about as the result of infectious or other illnesses, particularly if there is any lack of iodine, and it is apt to occur during puberty and adolescence, the times when changes in metabolism lead so frequently to glandular imbalance.

The principal difference between this and the hereditary deficiency is that the child has attained mental and physical development corresponding to the age before any symptoms occur. Usually the first thing that attracts attention is failure of the mental and physical development; the intellect becomes dulled, power of concentration is lacking, the speech is slow, and the memory poor. According to Simon (15), the advent of myxoedema in young people with a schizoid personality may precipitate a schizophrenic psychosis. The typical cretinoid facies is not present but the dull, stolid, broad face with thickened lips mirrors the inefficient brain; the complexion is pale, the skin cool and dry, and the hair is thin. In spite of a poor appetite, the patient increases in weight beyond the normal, but pads of fat as seen in cretinism are rare. The muscular weakness which is the reason for the easily occurring fatigue is shared by the heart muscle, so that dyspnoea may be present. Routine measurement shows that retardation of growth has

occurred, the amount varying with the length of time that the condition has been present, and radiographic examination shows that there is a corresponding degree of delay in ossification. In borderline cases, basal metabolic estimations are not satisfactory but determination of the creatine tolerance (16), which is increased in hypothyroidism, is of assistance. It is possible that the recently described galactose tolerance test (17) (25), which shows abnormally low curves in myxoedema, may prove to be of value. Sexual development shares in the general retardation, and in the female, if menstruation has begun, the cycle may be altered or menstruation may cease. Juvenile myxoedema is sometimes only temporary and clears up without treatment.

Treatment

This is conducted upon the lines already laid down, bearing in mind that the increase in bodily size demands an increase in the amount of thyroid gland. The administration of iodine may have little effect because of the diminished amount of thyroid tissue present, but a diet rich in protein, with low carbohydrate and a plentiful supply of fruit and vegetables is of considerable value. The increase of protein stimulates thyroid hyperplasia (18) and the bulky vegetable food aids peristalsis. Rapid improvement in the intelligence, strength, growth, and development of ossification occur with treatment, but the patient does not feel thoroughly well until the blood-count is normal. As a rule, it is found that thyroid function is so damaged that continuous treatment is necessary to avoid a relapse.

Atoxic Goitre : (a) Colloid or Simple Goitre ; (b) Nodular Goitre

The great majority of thyroid enlargements in childhood are atoxic in nature and occur commonly in those districts where the supply of iodine is poor. For clinical purposes, atoxic goitre may be divided into the colloid type, where there is a diffuse enlargement of the gland, and the nodular

type, where localised masses of thyroid substance cause irregularities on the glandular surface. As a rare occurrence, simple or nodular goitre is present at birth, usually in the children of goitrous parents, and may cause obstructed labour or a subsequent compression of the soft infantile trachea. In districts where goitre is endemic, enlargement is frequently observed in childhood and there is little difference in the incidence in boys and girls up to the age of puberty, but after that time girls are affected about six times as frequently as boys (19); shortly after puberty a goitre may appear, last for a year or two, and then disappear.

The cause of the enlargement is a lack of iodine sufficient for the needs of the individual. The frequent appearance of goitre between the ages of 14 and 16 years suggests that a greater amount is required when the gonads begin to function, and it seems possible that the increased metabolism which occurs in acute and chronic infections is the reason for the goitrous condition that appears subsequently. There is considerable evidence to support the theories that pollution of the water supply (20) and the presence of cyanides (found in cabbage) (21) may cause goitre by interference with the utilisation or absorption of iodine. The presence of fluorine is also associated with the development of endemic goitre (35).

Pathology of Colloid and Nodular Goitre

In an attempt to compensate for the lack of iodine with which to form thyroxin, the epithelium of the follicles undergoes hyperplasia, causing the thyroid gland to become two or three times its normal size. This abnormal proliferation of the parenchymatous cells is probably stimulated by an increase of the thyrotropic hormone of the pituitary gland. During this stage the amount of the colloid is reduced and the iodine content is lowered. With a decrease in the need for the hormone or an increase in the supply of iodine, involution occurs; this means that the gland becomes smaller as the proliferating cells become reduced in number. Coincidentally, colloid fills or distends the follicles and the iodine store becomes greater. At this point, when the

resting thyroid gland is somewhat larger than normal owing to the presence of a greater amount of colloid, the condition is known clinically as colloid goitre.

If the relative insufficiency of iodine becomes extreme, some of the parenchymal cells undergo exhaustion atrophy and the connective tissue of the gland becomes relatively and even absolutely increased. Recurring needs for iodine lead to alternate glandular enlargement and shrinkage, in the course of which some portions of the gland undergo hyper-involution, a condition in which colloid is stored in an amount sufficient to cause distension of the follicles. The nodules present in a goitre may be due to aggregations of such follicles or to remaining areas of hyperplastic tissue.

For further description of the above processes, the reader is referred to Marine (22).

Colloid Goitre

Usually there are no symptoms associated with colloid goitre unless the tumour becomes so large as to press on the trachea, oesophagus, blood-vessels, or nerves with symptoms referable to those structures; this lack of symptoms is chiefly because thyroid enlargements in children do not go down behind the sternum, where pressure upon mediastinal structures occurs easily. In the usual type of puberty goitre met with in adolescent girls there is a soft diffuse enlargement causing a fullness of the lower part of the throat. Any symptoms directly due to the enlargement can usually be traced to an under-function of the glandular tissue, causing slight myxoedema. The basal metabolism is usually within normal limits but is lowered if any myxoedema is present. There may also be a slight secondary anaemia. Menstrual irregularities such as dysmenorrhoea, increased flow or frequency, may be due to irregularity of function of a hyperactive pituitary gland.

The colloid goitre of adolescence should be recognised as a danger-signal indicating an endocrine imbalance that should be corrected. We have seen a number of cases of thyroid disease in later life who have given a history of having had a temporary enlargement of the thyroid at or about puberty.

The basal metabolic rate should be ascertained, and if it is lowered, thyroid gland should be given. It must also be remembered that there is a possibility of permanent thyroid defect and the patient or the relatives should be warned that there is a possibility of the development of hypothyroidism in pregnancy.

Treatment.—The prevention of colloid goitre can be ensured by attending to the purity of the water supply and the provision of an adequate supply of iodine in the water or in table salt (5 mg. of potassium iodide to each kg. of salt). Where goitre is prevalent, it is advisable that girls should be given iodine (8 to 10 mg. a week) for a year before the normal time for the beginning of menstruation and for a year or two after.

Once a goitre has developed, the results of treatment are not always successful. If the condition is mild, it can be treated by giving Lugol's iodine, minims 3 to minims 5 in water T.D.S. for some months, in order to prevent further enlargement of the gland and the formation of adenomata. Compression effects of these goitres seldom arise in childhood and adolescence so that the need for surgical treatment is rare. If the usual iodine treatment fails, it should be borne in mind that the pituitary gland may be at fault in not supplying sufficient thyrotropic hormone, one of the properties of which is to facilitate the removal of colloid from the thyroid. Means (23) reports the successful use of thyrotropic hormone in such a case.

Nodular Goitre

Although nodules of hyperplastic or colloid tissue are most frequently formed in adult life, they may occur at any time when the gland is passing through periods of hyperplasia or involution as the result of variations in iodine supply, and may even be present in infants in those regions where goitre is endemic. The clinical conditions associated with these tumours depend upon their size, situation, and number and the occurrence of degeneration, haemorrhage, or thyrotoxicosis. In some cases there are multiple small adenomata distributed generally throughout the gland, and

in others there may be gross asymmetry caused by a single large adenoma in which degenerative changes or haemorrhages have occurred. Symptoms vary according to the structure, which is compressed : pressure upon the trachea may cause considerable distortion of its direction and produce a frequent dry cough, tracheitis, or stridor, especially if there is bilateral enlargement ; substernal adenomata may press upon a bronchus, causing bronchiectasis or pneumonitis ; pressure upon the recurrent laryngeal nerve causes paralysis of a vocal cord, and pressure upon the sympathetic trunk produces enophthalmos, a narrowing of the palpebral fissure, and reduction in the size of the pupil. As thyroid adenomata are the end result of a recurring lack of thyroxin, it is to be expected that there will frequently be signs of hypothyroidism. Up to 10 per cent of thyroid adenomata eventually cause symptoms of thyrotoxicosis, a condition which is ultimately the same as Graves's disease, although in the toxic adenomas the thyrotoxicosis and the underlying pathological conditions are mild in degree and later in developing (24).

Treatment.—In view of the possibility of the subsequent development of thyrotoxicosis, the non-toxic nodular adenoma is best treated by surgical removal and any hypothyroidism is relieved by giving thyroid gland.

Hyperthyroidism

Excessive secretion of the thyroid gland may occur in two conditions : (1) Graves's disease, (2) toxic nodular goitre.

Graves's Disease

The occurrence of Graves's disease is rare below the age of 10 years, its onset taking place most commonly in children between 12 and 14. According to Reilly (36) it may run its course over many years during which there are periods of greatly increased activity followed by progressively longer periods of remission of activity ; there may be an occasional recurrence as late as the 30th year. It is encountered more frequently in females and there is a familial and hereditary tendency to its development. The pathogenesis of the

condition is unknown but the most commonly recognised precipitating cause is a psychic trauma (31).

Pathology.—The pathological changes seen in the diffusely enlarged thyroid in Graves's disease are smaller than those observed in the early stages of a simple goitrous enlargement. The cells of the acini undergo proliferation and become columnar in type and the amount of colloid becomes greatly diminished. Enlargement of the thymus gland is frequently observed but no changes in other endocrine glands have been consistently noticed.

Clinical features.—The child is highly emotional, sleeps badly, and may complain of palpitation. The most frequently encountered sign is tachycardia, which is unaccompanied by fever. An enlarged thyroid gland is present in nearly all cases and exophthalmos is observed in 75 per cent. Tremor is present and may be more generalised than in adults. Although the appetite remains good, a considerable loss of weight occurs and attacks of vomiting and diarrhoea are more frequent than in adults. The onset of the disease is frequently preceded by a rapid advance in skeletal growth with acceleration of the epiphyseal age and the teeth are often prematurely developed. Calcium and phosphorus studies have indicated demineralisation of the body and skeleton. The degree of these changes is in proportion to the activity of the disease. The onset of puberty is delayed by thyrotoxicosis. In girls, if menstruation has begun, amenorrhoea or scanty menstruation may result (36).

Diagnosis.—Confirmation of the diagnosis is obtained from the raised basal metabolic rate, the lowered blood cholesterol, raised blood iodine (26), and the occasional presence of a lowered sugar tolerance. The galactose tolerance test (17) (25) is stated to be more sensitive than the basal metabolic rate in cases of low-grade hyperthyroidism and is not influenced by hyper-ventilation induced by anxiety. Difficulty is occasionally encountered in the diagnosis of this condition from rheumatic carditis, especially if the latter is accompanied by a non-toxic goitre, but the raised temperature and normal B.M.R. should make the diagnosis clear.

Treatment.—The disease runs a relatively more benign and a shorter course than in adults and rest alone may be sufficient to cure mild cases. If it can be tolerated, a high fat diet with the addition of 3 g. daily of cholesterol is worth a trial, but whatever diet is used must contain more than the normal requirements of vitamin B₁ and vitamin A (27) (28) (29), for it is found that vitamin A is rapidly destroyed in hyperthyroidism and vitamin B₁ helps to prevent this destruction. If deep therapy is used, the thymus should be irradiated at the same time. Purely conservative methods of treatment are unlikely to be permanently successful in severe cases of Graves's disease and the prolonged costly invalidism, lack of schooling and child companionship at an impressionable age are unfavourable to normal physical and mental development. For such children, subtotal thyroidectomy after preliminary iodine treatment is the most satisfactory procedure. Post-operative myxoedema is less likely to occur in children than in adults because the remaining thyroid tissue will more readily hypertrophy in childhood and supply the normal need (37). It is not yet known why clinical cure results from removal of a portion of the gland. The restoration of health may be due to the re-establishment of a normal endocrine balance, which has been rendered possible by taking away the principal obstruction.

A typical case of hyperthyroidism in a boy aged 2½ years is reported by Crile and Blanton (30). The patient had persistent tachycardia, loss of weight, tremor, exophthalmos, goitre, muscular weakness, and nervousness. The blood iodine was 14·9 gammas per 100 c.cm., blood cholesterol 136 mg. per 100 c.cm., blood-sugar 132 and 182 mg. per 100 c.cm. The ossification and dentition were advanced, as one might expect from seeing the opposite occurrence in hypothyroidism. Subtotal thyroidectomy of a gland five times the normal size was followed by a successful recovery.

Toxic Nodular Goitre

Hyperthyroidism due to excessive secretion of a nodular goitrous enlargement is very seldom met with in childhood ;

the nodule may be present for years without causing any trouble, except possibly symptoms due to pressure effects. The signs and symptoms of toxicity develop slowly and are less severe than in toxic goitre; exophthalmos does not occur.

The treatment of hyperthyroidism due to a toxic adenoma is by operative removal of the tumour, after preliminary medication with iodine.

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CHAPTER 11

PARATHYROID CONDITIONS : THYMUS

Hypoparathyroidism

DISEASES of the parathyroid glands are conveniently considered as due to the lack or the excess of parathyroid hormone. (See Chapter 2.)

Very little is known concerning the causes of hypoparathyroidism. One or more of the glands may be removed accidentally in the course of thyroidectomy. Acute inflammation of glandular structure is rare and the presence of fibrosis, while sometimes due to inflammation or degeneration, can also be a natural occurrence owing to the increase of age.

Symptoms : Tetany

The most striking phenomenon which is associated with parathyroid insufficiency is the condition known as tetany, in which there is a hyperexcitability of the whole musculature, together with a liability to the spontaneous development of long-continued spasms. Tetany may be present either in a latent form or as manifest tetany. In its latent stage, the patient is fretful and may suffer from intestinal colic, tinglings, stiffness, and cramps of the arms and legs. Spasm of the facial muscles may be induced by tapping on the facial nerve just in front of the external auditory meatus (Chvostek's sign). Pressure upon the arm, sufficient to stop the circulation, will cause the appearance of Trousseau's sign, in which the fingers and hands are contracted into the position known as "accoucheur's hand". In the manifest stage, the spontaneous occurrence of Trousseau's sign is accompanied by a contraction of the leg and foot muscles which produces an equino-varus position of the foot (carpo-

pedal spasm). Cramp-like pains may occur on attempted movement and there may be difficulty in speaking. Strabismus may be present at times. In severe paroxysms the elbows are bent and the arms drawn across the chest, while the abdominal muscles may become rigid and the knees extended: the forehead, too, becomes wrinkled transversely and the corners of the mouth are drawn down, giving an appearance which has been likened to a carp's mouth. These signs may be accompanied by spasm of the glottis or diaphragm. Rarely, spasm of the glottis may be sufficiently prolonged to cause severe dyspnoea and even death. Generalised convulsions, of sudden onset, may occur, but are more frequently met with in infants than in older children.

A long-continued insufficiency of the parathyroid hormone causes trophic changes in the hair, teeth, nails, and the lenses of the eyes, as well as the effects upon the muscles of the voluntary and autonomic systems. The hair becomes sparse and the nails ridged and brittle; numerous observations have shown that the calcification of the dentine is characteristically altered and that the enamel of the teeth undergoes hypoplasia (1); the teeth consequently become ridged and lose their enamel. As a result of trophic changes in the protein of the lens, a cataract may develop, and it has been stated (2) that the majority of the cataracts in young people are due to this cause.

A considerable alteration in the metabolism of calcium and phosphorus is present in parathyroid deficiency. The serum phosphates are raised and phosphate excretion in the urine is diminished, possibly because one of the functions of parathyroid hormone is the ability to lower the renal threshold for phosphate excretion. A fall in the serum calcium takes place because of the failure in hypoparathyroidism to mobilise calcium from the bones. As a consequence of these failures in metabolism, neither calcium nor phosphorus are excreted in their normal amounts in the urine.

A satisfactory explanation for the production of tetany when serum phosphate is high and serum calcium is low is not yet apparent. The administration of a large amount of phosphate will produce tetany (3), and conversely a

diminution in the ingestion of phosphate-containing foods will decrease the liability to tetany. A low serum calcium is present in hypoparathyroid tetany, but tetany does not invariably supervene when the serum calcium is down to 5 mg. per 100 c.cm. (4). All things considered, the most important factor in the production of tetany in this condition is probably the increase of the serum phosphate which leads secondarily, in obedience to the law of mass action, to a decrease of calcium (5).

Other Conditions associated with Tetany

Tetany is not caused by parathyroid failure alone, but is met with in various conditions in childhood, owing, in the large majority of cases, to a disturbance in the metabolism of calcium and phosphorus. In rickets, the disease in which tetany is most frequently encountered, the inorganic phosphorus of the blood is lowered from 5 mg. per 100 c.cm. to 2 mg. per 100 c.cm. and the serum calcium is often normal (10 mg. per 100 c.cm.). If, however, the blood calcium falls, tetany is likely to occur. This may be precipitated by infectious diseases and by the addition of phosphorus to the diet; tetany may even occur when the rickets is healing (3). This disease is due to a failure in the absorption and utilisation of calcium and phosphorus in the absence of vitamin D, which is normally supplied in the food or synthesised from the ergosterol in the skin under the influence of ultra-violet light.

Coeliac disease is also characterised by the presence of rickets and the appearance of tetany, but in this condition the hypocalcaemia is due to a failure of absorption of fats, including the fat-soluble vitamin D, and the consequent formation of calcium soaps, so that calcium is only absorbed and used in minimal amounts.

Tetany may sometimes occur in renal dwarfism, a condition in which, following azotaemic nephritis, there is a high blood phosphorus and a relatively low blood calcium. As the parathyroid glands are known to undergo hypertrophy in this disease (6), it is possible that tetany is usually avoided by an increased secretion of parathormone.

The administration of excessive amounts of alkalis may induce tetany. This is generally believed to be due to a fall in the ionised calcium of the blood (7), because bicarbonates and alkaline phosphates can be shown to reduce calcium ionisation. Drucker and Faber (10), in investigation of the blood chemistry of children suffering from tetany, were unable to confirm this hypothesis. Frequent vomiting, as in pyloric stenosis and gastro-enteritis, and prolonged hyperventilation of the lungs such as may occur in hysteria and encephalitis lethargica, may also be followed by tetany, which is attributed to the lowering of the ionised calcium. Other diseases which should be borne in mind when considering the diagnosis are epilepsy, lead encephalopathy, and meningitis.

"Tetany of the new-born" may occur in children born of mothers who have exhibited symptoms of tetany during the later months of pregnancy, when the foetal demands for calcium, coupled with a low calcium diet, may induce relative hypoparathyroidism (8) (9).

In doubtful cases, when it is necessary to determine that hypocalcaemia is the cause of excessive nerve and muscle irritability, the patient is put on a low calcium diet for a three-day period. During this time the patient receives a weighed diet containing 0.1 to 0.2 g. of calcium and 0.75 to 1.0 g. of phosphorus per day and the daily twenty-four-hour specimens of urine are analysed for calcium and phosphorus. The blood is analysed for calcium and phosphorus on the fourth day or at any previous time if symptoms of hyper-irritability develop. Normal persons on such a diet excrete 0.19 g. of calcium for a three-day period and the serum calcium does not change, whereas individuals suffering from parathormone deficiency excrete about one-tenth of the normal amount of calcium and develop hypocalcaemia (9).

Treatment.—In all forms of tetany due to depletion of the ionised calcium in the serum, an attempt should be made to increase calcium absorption, beginning with the simplest measures. During the latent stage of the condition it may be sufficient to ensure that a calcium-rich diet is taken. Calcium lactate, in doses of 20 to 40 g. daily, may be taken in water or sprinkled on cereals. Absorption

of calcium is materially aided by giving vitamin D, supplemented if necessary by ultra-violet light therapy. Shelling (9) recommends that vitamin D should be used very cautiously in hypoparathyroidism, and then only when a high calcium diet is taken. If the diet does not contain more calcium than is normally taken, the use of vitamin D may provoke a rise in the blood phosphorus and a fall in the calcium, with a consequent liability to the development of tetany (9). MacBryde (11) has found that dihydro-tachysterol, a derivative of irradiated ergosterol, can be successfully employed over long periods of time in cases of severe parathyroid insufficiency. It acts by lowering the blood phosphorus and at the same time raising the blood calcium. The usual dosage is from 0.3 to 1 c.c. daily; when large doses are used, it is necessary to make frequent estimations of the serum calcium, at any rate until the maintenance dosage has been obtained, in order to ensure that the level is not being raised too high (12). The appearance of headache, nausea, and malaise are suggestive of over-dosage (13).

It must be remembered that the addition of foods containing phosphorus is likely to offset the advantage gained by an increase of calcium intake, so that it is advisable to omit milk and limit the meat and yolk of eggs and to increase the quantities of fruits, vegetables, and carbohydrates. For suitable low phosphorus diets, reference should be made to Shelling's monograph (9).

Prompt measures must be taken to relieve the symptoms of manifest tetany. For this purpose, 5 to 10 c.cm. of a 10 per cent solution of calcium gluconate may be given intramuscularly, or the more highly ionised Calciostab (Boots) by slow intravenous injection. Intravenous injections produce a very rapid and transitory effect, whereas intramuscular injections cause a rise of blood calcium lasting for about six hours. The intramuscular injection of parathormone in 10 to 20 Collip units twice daily produces a very rapid improvement, but unfortunately in some cases the effect is soon diminished or lost owing to the formation of an antihormone, so that it may become necessary to give many times this dosage or to give the parathormone intra-

venously instead of intramuscularly: at the same time, calcium must be administered orally to prevent bone absorption, and the serum calcium and phosphorus must be estimated from time to time to determine the maintenance dosage. In cases where tetany develops under apparently adequate treatment, enquiry should be made to ascertain that phosphorus-containing substances such as milk and cheese are not being added to the prescribed diet.

Magnesium, in the form of the carbonate, is useful because it has a depressant action on the nervous system, relieves the obstinate constipation, and helps in the excretion of phosphates. It has long been known that thyroid extract acts beneficially in hypoparathyroidism by stimulating the removal of calcium from the bones (14). It is possible that a synergic effect is produced by the combined parathyroid and thyroid hormones, for parathormone is found to cause a greater increase in the blood calcium in hyperthyroid patients than in normal people (15).

The transplantation of parathyroid tissue has given encouraging results when the tissue to be transplanted has previously been grown in the plasma of the recipient (16).

Good results are to be anticipated from adequate treatment and even the evidence of nutritional disturbances present in the teeth, hair, and nails may disappear (17).

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Hyperparathyroidism

The causes of hyperparathyroidism have been classified by Albright, Drake, and Sulkowitch (1) as follows :

- (1) Primary hyperparathyroidism due to a parathyroid adenoma and causing osteitis fibrosa cystica.
- (2) Primary hyperparathyroidism due to idiopathic parathyroid hyperplasia.
- (3) Parathyroid hyperplasia which compensates for phosphate retention in a certain type of renal disease.

Helfet (2) puts forward the theory that the function of parathormone is to control the level of blood phosphate, which it effects (a) by stimulating phosphate excretion by the kidney and (b) by mobilising calcium carbonate from the bones. Following this mobilisation, calcium phosphate is formed. An excess of phosphate in the blood, due to a change in phosphorus metabolism, stimulates the production of parathormone and, if long continued, leads to hyperplasia of all the glands. In conformity with this theory, hyperparathyroidism is divided into three groups :

- (1) Primary hyperparathyroidism due to an adenoma.
- (2) Secondary hyperparathyroidism :
 - (a) Compensatory or physiological, in which parathyroid hyperplasia is stimulated by retention of phosphorus.
 - (b) Pathological, in which an adenoma is superimposed on 2(a). Clinically, this is similar to the first group and reverts to the condition found in 2(a) after removal of the adenoma.

Primary Hyperparathyroidism

An excess of parathyroid secretion due to pathological hyperactivity of one or more of the parathyroid glands causes a removal of the calcium and phosphorus from the spongiosa of the bones and their rapid excretion in the urine. The effect of this constant loss of calcium phosphate is to

bring about an increasing rarefaction of the whole skeleton and in typical cases the formation of multiple cysts of bone which frequently become the sites of fractures.

Following the decalcification of the bones, the plasma calcium may rise to 29 mg. per 100 c.cm. and the excess is liable to be deposited in various viscera and the arteries, forming what is known as metastatic calcification. Although the phosphorus also passes into the blood-stream in greatly increased quantity, its blood-level does not rise but, on the contrary, sinks to below the normal limit of 2.5 mg. per 100 c.cm. because of the great excretion into the urine; this low plasma phosphorus continues as long as the kidneys are intact, but, when the power of elimination is weakened owing to the gradual destruction of the kidney substance by the formation of calcium phosphate stones, the level of the inorganic phosphorus tends to rise once more. As is usual in other conditions associated with an abnormal mobilisation of calcium from the bones, the phosphatase activity of the serum is found to be raised.

The phenomena of decalcification are not fully understood. In explanation, Jaffé (3) suggests that, in the first instance, minerals are withdrawn from the soft tissues and that the loss of minerals and the acidosis produced require compensation through the withdrawal of alkaline substances from the bones. When the calcium is removed from the bones, the osteoclasts increase in number and gradually remove the bone matrix, which is replaced by fibrous tissue.

As a general rule, not more than one of the parathyroid glands undergoes enlargement; the occurrence of hyperplasia of all the glands suggests the possibility that the diseased condition is secondary to some disorder affecting calcium and phosphorus metabolism. The histological appearances of the affected tissue are those of a hyperplasia of the normal structure, particularly involving the chief and eosinophil cells. In a typical case of advanced hyperparathyroidism there is a diffuse osteoporosis of the skeleton accompanied by localised cystic expansions of bone which have been produced by an encroachment of the process of absorption upon the cortex of the bone. Cysts, single or

multilocular, are more common in the long bones of the arms and legs than elsewhere but may occur in the skull, maxillae, ribs, pelvis, and in the bones of the hands and feet. Fractures may occur at these points of weakness. The softened vertebrae may yield to the weight of the body, causing kyphoscoliosis, and the pelvis may be distorted into the shape of a beak. The length of the body may be much reduced by shrinkage of the vertebrae and the arms and legs become diminished in length; the bones of the hands may become twisted and bent and the phalanges mere fibrous useless tags. The advanced disease, with multiple cysts and deformities due to mal-united fractures, is known as von Recklinghausen's disease (generalised osteitis fibrosa cystica). It is noted by Albright (1) that radiographic changes at the epiphyses are not present in this disease when it occurs in children.

The teeth, which do not constitute part of the reserve supply for calcium, are not affected by the general resorption and so form a marked contrast to the rarefied jaws in which they are embedded (4). It is stated that osteoporotic changes around the alveoli of the jaws may cause symptoms which are usually attributed to defects in the teeth, years before the final diagnosis of hyperparathyroidism is made (5).

Histological examination of the rarefied bones shows that the thinned-out spongiosa contains osteoclasts and that the bone is being replaced by fibrous tissue. The bone cysts are formed in a similar manner by destruction of bone and its replacement by fibrous tissue which often contains freshly formed spicules of bone. Sometimes these cysts contain areas of haemorrhage, either minute or very large in size, filling the whole cavity. The blood becomes changed to a brownish pigment, haemosiderin, and nests of phagocytic giant-cells are common; complete absorption of the blood may take place, leaving a cyst with loculi formed of fibrous walls.

Metastatic calcification causes its most serious effects when the kidneys are affected. Calcium phosphate stones are formed in these organs in about 70 per cent of cases of hyperparathyroidism, and it is also stated (6) that about

5 per cent of all cases of nephrolithiasis are caused by this disease. Up to eight times the normal amount of calcium phosphate is passed in the urine in high concentration, and some may appear in the urine as gravel or else form stones in the pelvis and body of the kidney, eventually causing inflammation which destroys the kidney substance.

Symptoms.—The presence of excess of calcium in the blood causes generalised muscular atony and weakness, bradycardia, loss of appetite, and constipation. Following the constant, uncompensated loss of calcium from the skeletal system, the bones ache, sometimes so severely that the patient cannot bear the pressure of bedclothes. The diuretic effect of parathormone (7) (8) causes polyuria and polydipsia, sometimes to such an extent as to simulate diabetes insipidus. Nausea, vomiting, and intestinal cramps which may occur are probably due to the continued loss of NaCl and water in the urine (9). At a later stage of the disease, cystic swellings may appear in the jaws or long bones, there may be fractures which fail to unite, and pain is constantly present in the back because the vertebrae become crushed by the weight of the body. Sooner or later renal colic is to be expected as a secondary complication.

Diagnosis.—The diagnosis is established by blood chemistry investigations and radiographic examination. The blood contains a raised calcium content and a decrease in the phosphorus. A considerable rise in the serum phosphatase is a further indication that resorption of bone is taking place. If the blood-changes are not marked, a calcium balance test is performed, placing the patient on a low calcium diet. For the method of carrying out the test and dietary details, reference should be made to articles by Bauer, Albright, and Aub (10). In such a test, the hyperparathyroid patient is found to excrete by the urine a great deal more calcium than is ingested.

Hypercalcaemia may be present in multiple myelomatosis, carcinomatosis or sarcomatosis of bones, and rarely in polycythaemia vera. Bence-Jones proteinuria may be absent for long periods in multiple myelomatosis, and in both this condition and that of metastatic carcinoma of

bones it may be necessary to resort to biopsy of the bone-marrow for confirmation of the diagnosis.

The radiographic appearances of osteitis fibrosa cystica are at some stages simulated by various diseases producing rarefaction of bone such as renal rickets, focal osteitis fibrosa cystica, osteomalacia, fragilitas ossium, Paget's osteitis deformans, multiple myelomatosis, the metabolic lipoidoses, hyperthyroid osteoporosis, and pituitary basophilism.

The distinction from renal rickets may prove extremely difficult in spite of the fact that chronic nephritis is the initial lesion, for it sometimes happens that parathyroid hyperplasia and even metastatic calcification are present. Focal osteitis fibrosa cystica is usually encountered in adolescents. It is not accompanied by changes in calcium excretion and usually becomes arrested. In osteomalacia, as in rickets, the osteoporosis is due to defective absorption and utilisation of calcium in the absence of vitamin D and there is no hypercalcaemia. Fragilitas ossium may cause confusion if the complete triad of symptoms, fractures, blue sclerotics, and otosclerosis are not present, but the calcium and phosphorus levels are normal in this condition. A rare familial and hereditary type of fragilitas ossium is associated with raised serum phosphatase and relative lymphocytosis (11). In Paget's disease the lesions are localised, the blood calcium and the urinary and faecal excretion of calcium are normal, although the blood phosphatase is high. Lipoid infiltration of the bones in Gaucher's disease and Niemann-Pick's disease may simulate the radiographic appearances of von Recklinghausen's disease, but the spleen and liver are enlarged and biopsy shows the presence of foam cells. Atypical cases of Hand-Schüller-Christian disease may be difficult to distinguish from a case of hyperparathyroidism in which the serum calcium is only slightly raised. In the former condition the serum phosphatase is normal, the blood cholesterol is raised, and foam cells are present in the affected areas of bone. The osteoporosis associated with hyperthyroidism and pituitary basophilism is a minor incident in these diseases and is unlikely to confuse the diagnosis. Another interesting though rare condition is osteitis fibrosa disseminata, in which

there are multiple bone cysts and areas of pigmentation. In female cases afflicted with this disease pubertas praecox has occurred, possibly due to a hypothalamic lesion. The blood chemistry in this latter condition does not show the changes associated with hyperparathyroidism (12).

Secondary Hyperparathyroidism

Advanced fibrocystic disease may occur in patients with normal calcium and phosphorus levels in the blood, although a calcium balance test shows that calcium output exceeds its intake. Such a condition is probably due to secondary hyperparathyroidism (2). In renal osteitis fibrosa cystica (1), a disease which is probably the adult counterpart of renal rickets, phosphate retention is present following renal insufficiency, the serum calcium level is normal or reduced, and extreme enlargement of the parathyroid glands takes place.

Treatment.—The accepted treatment of primary hyperparathyroidism is surgical removal of the affected tissue. This procedure may be very difficult owing to the occasional situation of a gland behind the trachea or behind the mediastinum. Enough parathyroid tissue to supply the normal requirements must be left (9). Following parathyroidectomy, the blood calcium falls rapidly and the urinary calcium excretion diminishes. In the immediate after-care it is necessary to keep a careful watch for the development of tetany, which may be caused by removal of too much parathyroid tissue, functional inadequacy of remaining parathyroid glands, or insufficient calcium or too much phosphorus in the diet. A temporary anuria may occur if the kidneys have been damaged by calcium deposits, and this will necessitate the intravenous administration of saline. Vitamin D should not be used unless excess of calcium is given in the diet, lest rapid bone calcification should lead to a sub-normal level of calcium in the blood.

The general results obtained are excellent. The patient recovers his appetite and vigour, loses the bone pains, and is no longer liable to the development of fresh calcium deposits in the kidneys. The bony deformities, however,

persist and the stones in the kidneys remain a source of danger to life.

When the hyperparathyroid condition is of the secondary type, either mild in degree and slowly progressive or persisting after the removal of hyperplastic tissue, Helfet (2) has found that the signs and symptoms may be alleviated by the administration of soluble aluminium salts which combine with phosphate in the food, forming an insoluble salt which is excreted in the faeces. A minimum of a pint of milk a day is added to the diet. The following mixture is recommended, with the caution that over-dosage may produce rickets :

Liq. Aluminium acetate (B.P.)	. 5 14	Ess. Cherry conf. opt.	. M 4
Syrup	M 360	Mel depuratum (B.P.) ad 54
Dose 3i q.i.d. p.c.			

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The Thymus

The thymus has long been the subject of controversy amongst physiologists and physicians. Recent experimental work on animals, either by extirpation of the glands over a series of generations or by intraperitoneal injections of a thymic extract, indicate that certain substances in the thymus, particularly those containing sulphur, contribute towards bodily growth, the myelination of nerve fibres, the maturation of the sexual organs, and possibly influence the calcification of bone. It is as yet undetermined how far

these conclusions are applicable to human beings and it is possible that the results obtained by giving thymus are due to the provision of a rich source of body-building material rather than to the presence of a hormone.

Thymic Hyperplasia

It is only of recent years that investigations based upon the examination of healthy children who have died as the result of accident have given an exact knowledge of the size of the normal gland. Previously its weight had been considerably underestimated because sufficient attention had not been paid to the possible effects of disease upon the gland, whereas it is now known that malnutrition, acute infectious diseases of a week's duration, and wasting illnesses such as tuberculosis and gastro-enteritis may produce considerable and rapid shrinkage.

The weight of the gland increases from the time of birth, when it averages 3 g., till the age of 15, when its weight averages 38 g. After this time it undergoes gradual shrinkage. It is to be noted that its weight, relative to the total weight of the body, is greatest at birth and that subsequently its increase in size fails to keep pace with the growth of the rest of the body (1). The increasing size of the thymus between birth and puberty is due to growth of the parenchymatous tissue; after puberty, both cortex and medulla show gradual shrinkage and are replaced by fat and connective tissue. It is presumed that this gradual relative decrease in the size of the organ is associated with a gradual waning of its importance.

The clinical estimation of the size of the thymus is usually a matter of some difficulty and even a radiological examination will not always settle the question, because the thymus is a mobile structure whose shape may undergo change owing to pressure, and in consequence the width of the shadow in the superior mediastinum shows fluctuations of up to 4 cm., varying with inspiration and expiration and with the phase of the cardiac cycle. Moreover, it may happen that apparent enlargement of the thymic shadow as seen in the radiogram is not substantiated by subsequent

examination *post mortem* (2). Occasionally it has been possible to demonstrate compression of the trachea through the bronchoscope (3).

Even a grossly enlarged thymus does not necessarily cause symptoms due to its size (2), possibly because of its mobility. It may, however, in the early days of life, cause attacks of dyspnoea, with pallor or cyanosis, accompanied by continuous stridor which is present during both expiration and inspiration and persists during sleep (4). The attacks may occur frequently and last only a few seconds, and as it is quite possible that the physician may not witness the event, it is necessary to bear in mind other causes of forced respiration such as deformity or tumours of the larynx, diphtheritic croup, retropharyngeal abscess, or macroglossia.

The cause of the sudden death which may occur in individuals having an enlarged thymus has not yet been elucidated. Post-mortem evidence of compression of the trachea and large vessels by the gland has been found so seldom that it is hardly likely that death takes place as a result of obstruction. A possible explanation is suggested by Selye's experiments upon rats with the object of determining the interactions of the thymus and adrenals under the influence of noxious agents (5). He found that severe trauma, shock due to operations, and the injection of atropine, morphia, or formaldehyde led to the rapid production of oedema of the thymus, which was shortly followed by degeneration of its cells and involution of the gland. At the same time, there was a loss of lipoid from the adrenal cortex and enlargement of the adrenals, attributed mainly to hypertrophy of the cortex. In a similar series of experiments on adrenalectomised animals it was not found possible to induce rapid involution of the thymus by damaging agents, whence it was concluded that the presence of some secretion from the adrenals is necessary for normal thymic involution. In view of these results, it seems possible that death due to the thymus may be caused by a sudden reaction of this type or a rapid failure of adrenal function.

Treatment of enlargement of the thymus.—In cases in

which gross enlargement of the thymus is causing stridor and dyspnoea it is justifiable to take advantage of the rapid effect produced by deep therapy. The technique of the treatment consists in the administration at one sitting of 40 to 80 roentgens filtered through 4 mm. of aluminium, with the thyroid protected. Doubt has, however, been expressed as to the ability of deep therapy to prevent death due to the thymus (2).

Status Thymicolymphaticus

This condition was first described by Paltauf (6) in cases in which sudden death occurred during emotional strain, general anaesthesia, or as a result of trifling injury. At autopsy these subjects were found to have an unusual amount of subcutaneous fat, enlargement of the thymus and increase in the lymphoid tissue of the intestines, lymphatic glands, spleen, and tonsils. In some cases there was an associated hypoplasia of the vascular system, characterised by narrowness of the lumina of the great vessels and thinness of their walls; this hypoplasia sometimes coincided with poor development of the chromaffin system. Clinically these patients were noticed to be pale and fat and to be liable to infections of the skin and mucous membranes, while some of them showed poor development of the genitals and of the secondary sexual characteristics. It is noticed that the original observer did not think that the enlarged thymus was the prime cause of the sudden death and it was suggested that there was an inherent weakness in persons having this diathesis. Other investigators (1) have observed that an enlarged thymus is not of necessity associated with a general increase of lymphoid tissue and that there appears to be no correlation between thymic hypertrophy and vascular hypoplasia. More recently, the view has been advanced that sudden death in this condition is explicable on the assumption that there has been anaphylactic shock caused by sensitisation to proteins derived from necrosis of the germinal centres of the lymphoid tissue (7).

At present there is no general agreement as to the

existence of a lymphatic diathesis as a pathological entity, but it is possible that an increase in knowledge of the factors producing enlargements of the thymus and lymphatic tissues may reveal that we are here dealing with a fresh group of diseases.

Enlargement due to other Causes

The thymus is enlarged and fails to undergo its normal involution in hypogonadism, hypopituitarism, and cretinism, all of which conditions are primarily or secondarily associated with a lack of maturity of the gonads and delay in the formation of the secondary sexual characteristics. Enlargement of the thymus is often present in Addison's disease (8), a coincidence which may possibly be linked with the apparent antagonistic action between the thymus and adrenals, as demonstrated by Selye's experiments (see above), and the presence in the adrenal cortex of a substance which is capable of influencing the development of the secondary sexual characteristics, amongst which should probably be included the normal involution of the thymus (cf. physiology of adrenal cortex).

Tumours of the Thymus

The presence and effect of tumours or hyperplasia of the thymus in certain cases of myasthenia gravis is very difficult to explain in the light of present knowledge of the function of the thymus. We can only assume that the condition which caused the myasthenia has also been responsible for changes in the thymus.

The reason for the occasional presence of tumours of the thymus in cases of Cushing's disease is no less difficult to elucidate. Apparently the only abnormality which is common to all cases of this syndrome is a conspicuous amount of hyaline change in the basophil cells of the anterior lobe of the pituitary gland, whether the disease is associated with a basophil adenoma of the pituitary, a neoplasm of the thymus, or a neoplasm or hyperplasia of the suprarenal cortex (9) (10). It is possible that the essential lesion producing this clinical syndrome is originally caused by

abnormal hormonal stimulation arising in any of these endocrine glands.

It has long been known that thymic tumours are present in a large proportion of cases of myasthenia gravis and it has been claimed (see p. 45) that thymus implants in dogs will produce a severe myasthenic reaction. Recently, Carson and Keynes (11) have reported upon the treatment by thymectomy of twelve patients in whom the symptoms were so prolonged and severe that a spontaneous remission of the disease was unlikely. Most of the patients had been given an injection of prostigmin prior to operation, and had shown the increase of strength which is the typical myasthenic response. The results were successful in three cases who became able to lead normal lives. Two patients did not subsequently exhibit the myasthenic response to prostigmin. In others, the remission was partial and prostigmin was necessary, though in reduced doses. It was suggested that the whole of the thymic tissue might not have been removed in the latter group of patients.

The striking improvement obtained by removal of the thymus in the above cases of myasthenia gravis gives support to the suggestion (p. 45) that the thymus has some effect upon the metabolism of acetylcholine.

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- (11) Carson and Keynes, *Proc. Roy. Soc. Med.*, 36: 140, 1943.

CHAPTER 12

DIABETES MELLITUS: HYPERINSULINISM

Diabetes Mellitus

DIABETES MELLITUS is a condition due to deficiency of the internal secretion of the pancreas. It is characterised clinically by excessive thirst, polyuria, wasting, and a liability to the development of coma, and pathologically by the presence of hyperglycaemia and glycosuria.

Diabetes is rare in infancy and childhood; at this age there is a more rapid onset than in adults and a greater severity of the symptoms with quicker progress to a fatal termination. A strong hereditary influence plays a part, shown by the occurrence of diabetes in identical twins and by the results of the examinations of the blood-sugar curves of the relatives, in whom hyperglycaemia is frequently found; in fact the familial incidence has been shown to be as high as 35.1 per cent (1). Pincus and White (2), on examination of the family histories of 523 diabetic patients, came to the conclusion that the potentiality for diabetes is inherited as a simple Mendelian recessive. The children of diabetic mothers are rarely diabetic at birth; on the contrary, they may be over-weight and show symptoms of hypoglycaemia, caused by an increase in the size and number of the islet cells (3) (4).

The adult type of diabetes is commonly preceded by obesity, but in juvenile diabetes overgrowth is the most common precursor, not excepting those patients in whom dwarfism is present (5). Bogan and Morrison (6) also found that the average osseous development was eighteen months in advance of the chronological age and that the dental development was twelve months in advance. All these

findings suggest that juvenile diabetes is preceded by hyperactivity of the anterior lobe of the pituitary gland. This evidence of hyperactivity rarely persists throughout the disease ; after several years the height and weight have become normal or even subnormal for the age, and this slowing of growth is attributed to a decrease in the activity of the pituitary gland. In consequence the juvenile diabetic frequently comes under observation for the first time when signs of dwarfism are already present. The physical characteristics of these patients are typical of hypopituitary dwarfism, viz. the height is below normal and the upper measurement may be longer than the lower measurement ; the skin is thin and often covered with down ; the osseous development is normal or delayed and epiphyseal closure is late. Puberty is usually delayed till the age of 17 years. White (5) found, in the cases of 36 diabetic dwarfs, that the data for the height indicated that the subjects were originally tall diabetic children.

Morbid Anatomy

In juvenile diabetes it is rare to find changes in the islet tissue that are irreversible. Aplasia of the islets has been described (7) and hydropic degeneration is occasionally found (8). In some cases there is an eosinophilic (3) or lymphocytic (8) infiltration of the islets ; in others, there is cirrhosis of the pancreas with islet destruction (9).

The changed metabolism of carbohydrates is responsible for abnormal distribution of glycogen. In the liver, glycogen is normally stored in the cytoplasm of the cells ; in diabetes, it is found mainly in the nuclei. The skin and skeletal muscles are deprived of glycogen, there is an excess in the cardiac muscle, and glycogen is found in the tubules of the kidney. Alteration in fat metabolism is strikingly evident. The reticulo-endothelial system of the spleen is loaded with lipid, the liver is commonly enlarged owing to fatty infiltration, and atheromatous changes are frequent in the heart and blood-vessels. The kidneys, in addition to the abnormal deposits of glycogen in the cells of the tubules, are found to be mildly sclerotic. Clinically, the urine

contains numerous casts and traces of albumin and nitrogen retention may occur.

Symptomatology

The disease may occur at any age and in children is most frequently encountered between the ages of 10 and 15 years, boys being affected more often than girls. In adults diabetes is usually slow in onset, but in juveniles the disease may be so rapid in onset and progress that the whole course may extend over a few days only. Joslin has suggested dividing the types of onset into the following groups, according to the speed with which symptoms are manifested :

- (1) *Indefinite*, when the development of symptoms is so slow that no certain time of onset can be established.
- (2) *Gradual*, if the symptoms have developed over a period of eight weeks.
- (3) *Rapid*, if in the course of seven days.
- (4) *Sudden*, if on a particular day.

In infancy the onset is usually gradual, developing over a course of about eight weeks. An increased frequency of micturition is accompanied by unusual thirst ; there is listlessness, rapid exhaustion when taking exercise, a poor appetite, and a progressive diminution in weight. Pruritus may be troublesome, especially in baby girls, and it may be noticed that the napkins are stiff with sugar from urine passed during the night. Digestive disturbance and constipation are common. The urine contains glucose and possibly ketone bodies, and a glucose tolerance test shows that there is hyperglycaemia with a diabetic type of blood-sugar curve.

The course of the disease is more severe in infancy than in later childhood and adolescence, possibly because growth takes place more rapidly in early life and the area of the body surface proportionate to the weight is greater in infants, necessitating a heightened metabolism and a greater production of insulin.

Polyuria

As a general rule, the first sign of diabetes is the development of polyuria, some two to four litres of urine being excreted during the twenty-four hours. The elimination of such a large quantity of water is brought about not only by the excess of sugar in the blood but also by the presence of the sodium and ammonium salts of the diacetic and beta-hydroxy-butyric acids which are formed during the incomplete combustion of fats which occurs in uncontrolled diabetes. The specific gravity of the urine is high, usually between 1030 and 1040, owing to the presence of 2 to 5 per cent of sugar. In infants, the constant presence of an irritating urine will probably cause excoriation of the skin of the thighs; if there is any difficulty in obtaining urine for test purposes, enough can be recovered by wringing out the napkins. The unchecked loss of water and sodium leads to dehydration of the body tissues and causes extreme thirst, accompanied by dryness of the pharynx, headache, and dizziness.

Glycosuria

The finding of glucose in the urine is not necessarily evidence of the presence of diabetes mellitus. In some individuals the ingestion of large amounts of sugar may cause a temporary hyperglycaemia and overflow into the urine. Glycosuria may also be present during the febrile period of infectious diseases and may occur in any person when carbohydrate feeding follows lengthy starvation. Of more practical importance is the recognition of renal glycosuria, a condition of hereditary and familial origin in which persistent glycosuria occurs owing to a lowered renal threshold. The blood-sugar curve is normal, and although pruritus and enuresis may occur, no further signs of diabetes are present and the incidence of true diabetes amongst subjects of renal glycosuria is no greater than among the rest of the population (10).

Apart from lactose, which is found in pregnancy urine, the only other sugars which occur are pentose and fructose,

and these are pathological rarities. Certain other reducing substances are more frequently found in the urine, and one of importance is glycuronic acid, which is excreted in a conjugated form after the administration of phenolic drugs. This may lead to serious errors of diagnosis if the patient has been taking large amounts of aspirin. Another reducing substance encountered in all cases where intestinal fermentation is present is indican.

The glucose excreted is derived principally from the carbohydrate ingested, its amount varying with the quantity of the carbohydrate and the form in which it is supplied. Sugars are most rapidly absorbed and excreted, the effect of starchy foods is less, and that of fruits and vegetables is least noticeable. In severe, uncompensated diabetes, both food and tissue proteins are broken down into products from which glucose can be formed, and if more protein is so utilised than is ingested, very rapid wasting occurs.

Hyperglycaemia

The changes in metabolism that are due to the insufficiency of insulin are mirrored in the alteration of the contents of the blood-stream. The most important is the variation of the blood-sugar curve after a test dose of sugar. Compared with the normal, the fasting blood-sugar is at a higher level, and after the administration of a measured dose of sugar, the peak, which may be at a level of over 300 mg. per 100 c.cm., is gradually reached in two or more hours; at the point where it passes the renal threshold for sugar, glycosuria occurs and continues as long as the blood-sugar is above threshold level; subsequently, the blood-sugar falls slowly and does not reach its previous level until four or more hours have passed. With increasing duration of the disease, the renal threshold for sugar may rise from the normal, 170 mg. per 100 c.cm. to 300 mg. per 100 c.cm., a condition which may allow of the presence of severe hyperglycaemia without the coincident passage of sugar into the urine. It is normal for the whole blood-sugar curve to be at a lower level in infants and young children than in adults. Between the ages of 5 weeks and 3 years the fasting level

may be normally 65 mg. per 100 c.cm., and the highest level may be reached at 95 mg. per 100 c.cm. at the end of an hour (11), as estimated by the method of King and Hazelwood (19). This method estimates true glucose and consequently the figures are 28 mg. per 100 c.cm. lower than those usually accepted, and is the method used in this book.

Hyperglycaemia is not in itself sufficient to justify the diagnosis of diabetes. It may occur as a result of muscular exertion, a febrile state, excitement, and heavy smoking, and may be present as a more permanent effect in certain endocrine abnormalities. In some cases of hyperthyroidism the blood-sugar may rise rapidly above the kidney threshold and cause glycosuria, but the return to the fasting level occurs within two hours. It is only rarely that both diabetes and hyperthyroidism are present at the same time, and then the hyperthyroidism usually precedes the diabetes. In these cases the glycogenolysis of hyperthyroidism is added to the insufficient oxidation of glucose caused by diabetes and control of the condition by diet and insulin becomes very difficult. During the early stages of acromegaly, when the pituitary is enlarging and hyperactive, the patient may have hyperglycaemia and glycosuria, possibly as a result of the outpouring of thyrotropic and diabetogenic hormones.

Ketosis

The failure of carbohydrate metabolism in the diabetic patient leads to a partial breakdown in the metabolism of fats and proteins. In the absence of available carbohydrate, the fats are not broken down completely into carbon dioxide and water, with the result that the ketone bodies, acetone, diacetic acid, and beta-hydroxy-butyric acid are produced and the body has to call upon its reserves of bases for correcting this condition of acidosis which is tending to alter the hydrogen ion concentration of the body fluids and tissues. Ketones are also produced in the diabetic by the catabolism of amino-acids such as leucine, phenylalanine, and tyrosine. The first ketone to appear is acetone, which is present in the breath and urine ; subsequently, ammonium and sodium

salts of the above-mentioned acids appear in the urine. As a result of the continued neutralisation of acids and their conversion into salts which are excreted, the plasma becomes deprived of its bases and the carbon dioxide combining power of the blood is reduced; acidosis is present when the alkali reserve has been reduced to less than 50 c.cm. of CO_2 per 100 c.cm. of plasma.

Coma

A minor degree of acidosis is not uncommonly found as a symptom of exhaustion in children, but in the diabetic it is a danger signal which may easily be the precursor of a rapidly fatal coma. As a cause of death in juvenile diabetes, this easily ranks first, being still accountable for 43 per cent, although it has steadily decreased since the discovery of insulin (12). Coma is caused by the absence of sufficient carbohydrate to prevent the incomplete combustion of ketone bodies. It may be precipitated by a failure to observe the prescribed dietary régime, by slight as well as severe infections, and by starvation. It is commonly preceded by pain, which may take the form of headache, pains in the legs or abdomen, and is ushered in by restlessness, thirst, polyuria, and loss of appetite; as the condition develops, there is vomiting and a heavy smell of acetone in the breath; hyperglycaemia is present and may eventually rise to over 470 mg. per 100 c.cm. and the urine may contain more than 4 per cent of sugar, a trace of albumin, and a few casts, in addition to large quantities of acetone and diacetic acid; later on, the pulse becomes rapid, the temperature falls, the breathing becomes slow and deep, and there is increasing mental torpor accompanied by abolition of the tendon reflexes and incontinence. With dehydration the intra-ocular tension falls, a leucocytosis occurs, and inspissation of the blood causes a decrease in the peripheral circulation which may prevent the loss of body heat, resulting in a final rise of temperature. Convulsions, especially in the infant, may be the final result.

Lipaemia

An excess of cholesterol and lipoids in the blood is characteristic of failure of the control of the diabetic state. Although cholesterol is not a fat, its production runs parallel with the quantity of the blood lipoids and the estimation of the blood cholesterol forms the readiest indication of the lipid level. Over-nutrition, extreme variations of weight from the normal standard, and acidosis of any considerable degree are associated with an excess of cholesterol, the upper normal of which is 230 mg. per 100 c.cm. in children (10).

Complications of Diabetes

The diabetic is liable to infection which is not explained by an excess of glucose in the blood. It is possible that there may be a defective production of antibodies, for it has been shown that the formation of agglutinins is delayed (13). Even in normal people there is a decrease in the sugar tolerance during infections, and in diabetics it is found that bacterial invasions of any kind necessitate greatly increased amounts of insulin. Boils and carbuncles are comparatively easily dealt with: the occurrence, however, of pulmonary tuberculosis, which, while not more frequent amongst diabetics than in the general population, is becoming more frequent among diabetic children now that their span of life is being prolonged (12), is peculiarly dangerous, because of the inconstant fluctuations which it causes in the blood-sugar over a long period of time, which interfere with the regularity of the recurrent insulin need.

The major manifestations of the atherosclerotic lesions frequently met with after the age of 55 are only rarely encountered in children, although diabetic children do show an abnormal increase of atheromatous deposits, and calcification of arteries has sometimes been demonstrated radiographically. The possibility of a diabetic origin of gangrene must be kept in mind, as is shown by the case-history of a child who, at the age of 9 days, had extensive dry gangrene of the left leg and a concomitant pancreatitis with acute

degeneration of the islets of Langerhans (14).

Children are less subject to skin lesions than adults, but they are more liable to the interesting condition of xanthosis, in which there is a yellowish colouration of the skin, especially of the palms and soles. This colour is due to excess of lipochrome formed from ingested carotin, which in the normal liver is converted into vitamin A (15). Blood-serum carotin curves in diabetic children show that carotin is not eliminated as rapidly as in normal controls (16). This condition is met with in cases of progressive diabetes and indicates a grave prognosis.

Enlargement of the liver is sometimes found in severe cases and may be accompanied by jaundice. Xanthomatous nodules, cataracts, and the presence of diabetic neuritis are only very rarely found.

Treatment

The following method of treating diabetes is the one which we have used for years. It involves blood-sugar estimations, which we consider essential for adequate control of the condition in children. The same procedure is followed whether symptoms are mild or severe, unless the patient is in coma or bordering on it (see p. 257).

The patient is weighed, put to bed, and a diet consisting of a number of lines from Lawrence's diet scheme (17) is given. We have printed and explained the scheme on pp. 88 and 89 and will only briefly summarise it here.

Each line consists of a carbohydrate half-line containing 10 g. of carbohydrate, and a protein and fat half-line containing $7\frac{1}{2}$ g. of protein and 15 g. of fat. These were the quantities as published in 1936, but since then Lawrence has found it advisable to reduce the quantity of fat in the ration, so that now the protein and fat half-line only contains 9 g. of fat. On the diet scheme (p. 88) the quantity of fat corresponding to 9 g. is given in the extreme right-hand column, and in treating diabetics this column should be used for calculating the fat ration. With this modification the diet scheme on p. 88 is almost the same as

Lawrence's most recent scheme.¹ This reduces the caloric value of a line to 155 calories. One black portion (10 g. carbohydrate) gives 41 calories and one red portion (7½ g. protein and 9 g. fat) 114 calories. In consequence Table B (p. 90) for calculating the number of lines required is not applicable, but a diet containing a given number of calories of carbohydrate, protein, and fat can easily be calculated from the above figures.

We retain the 1936 scheme for the general treatment of obesity because it provides a higher caloric value with relatively less starch than the modified diet. As a start the diabetic child is given a diet containing less than his normal caloric requirements, say from 5 to 10 lines, according to his weight and age. Symptoms usually improve as soon as the patient takes a balanced diet of this type. In order to determine the severity of the condition and to obtain guidance in giving insulin, a four-point blood-sugar curve is constructed. This is plotted from an estimation of blood-sugar at four times during the day, usually after breakfast, at noon, at 3 P.M., and at 5 P.M. At the same times the urine is tested for sugar by Benedict's solution and acetone bodies by Gerhardt's test. In severe cases it may be an assistance to have the points on the curve closer together or to plot them throughout the night, but as a rule this is not necessary. This simple scheme shows clearly how the pancreas is dealing with sugar during the day, and from the fasting blood-sugar and the early morning specimen of urine some idea can be obtained of what has been happening in the night. The four-point curve can be repeated to see the effect of changes in diet and insulin, and in this way is of great value in controlling treatment. This curve should be distinguished from a glucose tolerance curve, which shows how the pancreas deals with a single dose of sugar and is of particular value in distinguishing renal glycosuria from diabetes.

The next step is to give insulin, which is always required in children, the dose depending on the results of the four-

¹ The line ration scheme may be obtained on a convenient card from Messrs Lewis, Gower Street, London, W.C.

point curve. In a moderately severe case 10-15 units of soluble insulin are given before breakfast and before tea or supper, and the urine is tested in the early morning and after each meal. Five units of soluble insulin are added daily to the dose either in the morning or evening, as appears most appropriate from the urine tests, until the urine is free or almost free from sugar during the whole twenty-four hours. This process rarely takes longer than a week, and meanwhile all symptoms greatly improve and acetone diminishes in the urine, although it may not entirely disappear while the patient is taking an inadequate diet. If a four-point blood-sugar curve is repeated when the urine is sugar-free, a considerable drop in the blood-sugar level will be found, but it will still be above normal in all but the mildest cases, because of a raised renal threshold to sugar. For this reason we usually do not plot a curve at this stage but continue for several days with the same diet and insulin dosage in order to obtain as nearly as possible a normal blood-sugar level. Careful watch must be kept for symptoms of hypoglycaemia, for this is the period when it is most likely to occur; but it need not occasion alarm, for in children it is rarely dangerous even when severe. If symptoms of hypoglycaemia appear, a four-point curve is plotted at once, otherwise it is done after an interval of three or four days, and this curve is compared with the first one. In the mild case the result may be normal; in the more severe case normal may be approached but further adjustment of diet or insulin dosage will be necessary. The four-point curves give the treatment a precision which is entirely lacking if laboratory control is not available. As soon as the four-point curve is approximately normal, the diet is increased by adding a line or half a line at a time, and it is usually found that considerable addition to the starch ration can be made at this stage without increasing the insulin dosage. But, if necessary, more insulin must be given to allow of an adequate amount of carbohydrate, and it must be remembered that a further 10-20 g. is taken in the vegetables listed on the diet scheme as containing a negligible amount of starch. The protein and fat are also increased until a satisfactory diet for the

size and appetite of the patient is obtained.

The patient is now properly controlled on an adequate diet with soluble insulin, probably in two doses. The next stage in treatment is the substitution of insoluble for soluble insulin. In the mild or moderate case of diabetes where there is no great excursion of blood-sugar level, one slightly smaller dose of insoluble insulin is substituted for the two doses of soluble insulin. For example, if the patient had been taking 25 units of insulin twice a day, 45 units of insoluble insulin might be substituted in one dose, usually given before breakfast. Insoluble insulin is absorbed much more slowly than soluble insulin, so that there is a continuous effect on the blood-sugar over many hours, thus obviating the necessity for repeated injection. In a mild case one dose may suffice and the treatment has then been reduced to its simplest form, but in most children one dose is not sufficient, for a peak of hyperglycaemia will remain at one or more points in the twenty-four hours, probably immediately after a meal, which cannot be controlled by the slow-acting insoluble insulin. Soluble insulin is then used in addition, given just before the rise is due to take place. Utilising in this way the continuous effect of one variety of insulin, the quick effect of the other and the buffering action of extra carbohydrate meals where required, the majority of severe diabetics can be controlled. The action of insoluble insulin varies very much from one person to another and therefore it is usual to stabilise the patient first with soluble insulin which has a more predictable action.

Now that the patient has been stabilised in this way he is allowed to get up and the question of exercise taken into account, for this increases the metabolic process and may precipitate hypoglycaemic symptoms. The child then returns to normal life and the mother is given the following instructions: to adhere to the Lawrence's line diet and the proper dose of insulin, to test the urine daily, to watch for signs of hypoglycaemia, to call in her doctor at any time for infections, so that the necessary adjustment of diet and insulin may be carried out, and to bring the child back for blood estimations at appropriate intervals, which vary with

the severity of the disease. It is generally possible to allow the mother to stop weighing the protein and fat ration, the amounts of which she may guess when she has had a little experience, but the importance of weighing the carbohydrate must be impressed upon her. The subsequent conduct of the case follows the same lines with gradual increase of diet as required by growth, and adjustment of insulin dosage with the help of urine and blood-sugar tests. The point which we stress as of the greatest importance in the treatment of diabetes is the necessity of giving enough insulin to keep the blood-sugar within normal limits. If this is done, rapid reduction of insulin dosage is sometimes possible owing to the restoration of islet function. Nothing is easier than to treat diabetes in a slipshod fashion, for symptoms are easily relieved by a restriction of starch and an inadequate dose of insulin, but it is most reprehensible to treat children in this way, for unless they are properly controlled, disaster inevitably ensues.

The fear of hypoglycaemia prevents the proper use of insulin in many cases. This should not be so, because the danger is slight in children and symptoms of hypoglycaemia indicate restoration of islet function. It is rare for severe symptoms to develop without warning having occurred at the same time for several preceding days, and it should be remembered that almost any recurring symptom may be due to hypoglycaemia. We do not advocate high carbohydrate diets, because experience in children and adults in other disorders has convinced us that present-day diets contain too much starch even for those whose carbohydrate metabolism is normal, and we therefore feel that we should restrict it where the carbohydrate metabolism is at fault. We allow about 130 g. of starch *per diem*.

In the above account we have assumed that laboratory control of the condition is available, but if this is not so, what is to be done? The scheme outlined above should be adhered to as closely as possible, using frequent urine tests, which give a lot of information if correct deductions are made. For example, if the early morning specimen of urine contains sugar, all we can deduce is that some time during

the night the blood-sugar rose above the renal threshold ; but if a second specimen be examined before breakfast, a fair idea may be obtained of the level of the fasting blood-sugar. Similarly, specimens examined after food will show if the insulin dose is adequate. More care must naturally be taken in increasing insulin dosage and extra precaution shown in keeping watch for the clinical signs of hypoglycaemia.

The following case reports will illustrate the above instructions :

CASE No. 135.—A girl, aged 13 years. This child had lost weight for six months and lately had complained of thirst. The maternal grandfather had died of diabetes. The urine contained a large amount of sugar and a blood-sugar estimation three hours after a meal showed no less than 0·615 per cent of sugar. She was admitted to hospital at once. Fifty units of soluble insulin with 2 oz. of glucose were given, followed by a 7-line diet and 20 units of soluble insulin twice daily. Four days later the fasting blood-sugar was 0·115 per cent. A month later, when she was having a 9-line diet and 10 units of soluble insulin twice daily, the blood-sugar values were as follows :

Fasting	.	.	0·047 per cent
12 noon	.	.	0·085 „
3 P.M.	.	.	0·100 „
5 P.M.	.	.	0·077 „

Within a fortnight she was suffering from hypoglycaemic reactions of a mild type in the evening, and the soluble insulin was reduced to 10 units in the morning and 5 in the evening, while the carbohydrate ration was increased from 90 to 100 g., and the extra starch was given at tea-time.

This patient shows that the initial level of the blood-sugar must not be taken as a criterion of the severity of the disease, and shows the rapid improvement which often takes place as soon as proper treatment is instituted. During the following year the child grew and gained weight on the same diet. After a few months the blood-sugar started to rise and the dose of soluble insulin was gradually increased to 30 units twice daily by the end of the year. During the whole of this time she had no symptoms and sugar was only occasionally found in the urine, usually in small quanti-

ties. This illustrates the great difficulty of treating these patients without blood-sugar estimations, for the rise in renal threshold for sugar may mask hyperglycaemia.

With increasing doses of insulin the blood-sugar was fairly well controlled but remained somewhat high. A gradual rise in insulin requirements after the first stabilisation often occurs in children, but it reaches a peak and then usually remains steady for a long period, the ultimate insulin requirements depending on the degree of recovery in the islet tissue of the patient's pancreas.

CASE No. 136.—A boy aged 16 years. At the age of 12 years he had been in hospital for diabetes; a glucose tolerance test showed a climbing type of curve reaching 0.32 per cent sugar at the end of two hours. He had been sent out of hospital on a 7-line diet and 5 units of insulin twice daily. Four years later he came again, complaining of pain in the right cheek and eye. Under the care of the ophthalmic and aural surgeons a gangrenous eyeball was removed together with necrotic bone from the orbit. The wound was drained and later a repair operation was carried out. On admission to hospital aged 16 years, the blood-sugar varied from 0.2 per cent to 0.3 per cent during the day up to 6.0 per cent of glucose in the urine on a 7-line diet. Great difficulty was experienced in stabilising the patient, for extreme variations in blood-sugar occurred. Soluble insulin was gradually increased up to 50 units in the morning and 45 in the evening. Then 45 units of soluble and 45 units of insoluble insulin were given in the morning. The effect of this dosage can be seen in the following table of blood-sugars:

9 A.M.	.	.	0.066 per cent sugar	.
12 noon	.	.	0.086	" "
3 P.M.	.	.	0.087	" "
5.30 P.M.	.	.	0.212	" "
9.30 P.M.	.	.	0.228	" "
1 A.M.	.	.	0.200	" "

To correct this curve 30 units of soluble insulin were given in addition before supper with good results, as shown by the following table:

6 P.M.	.	.	0.136 per cent
1 A.M.	.	.	0.046 "
6 A.M.	.	.	0.074 "

All urine specimens were free from sugar and the patient was kept

on this very large dose of insulin for thirteen days, when the curve showed a remarkable improvement :

9 A.M.	.	.	0.030 per cent
12 noon	.	.	0.085 ,,
5 P.M.	.	.	0.071 ,,
9 P.M.	.	.	0.032 ,,
12.30 A.M.	.	.	0.035 ,,
6 A.M.	.	.	0.078 ,,

The patient was now controlled throughout the twenty-four hours—in fact some of the blood-sugar figures were dangerously low and in consequence the carbohydrate ration was raised to 100 g. from 70, and he was given 50 units of insoluble and 45 units of soluble insulin in the morning and the evening dose of soluble insulin omitted. He was discharged from hospital. Unfortunately he did not attend for observation nor did his parents think it necessary to take any action until after the last of three severe hypoglycaemic reactions which occurred six weeks after leaving hospital. In the first of these attacks he had a sudden paralysis of the right side with aphasia lasting one and a half hours. In the second he became unconscious suddenly for the same period with much sweating; the third attack was similar, after which he was admitted to hospital. By then he had recovered following administration of sugar. The next morning the fasting blood-sugar was 0.214 per cent, so he was given 30 units of protamine with 30 units of soluble insulin and 20 units of soluble insulin in the evening. A curve following this dosage showed some most remarkable figures as follows :

9.30 A.M.	.	.	0.005 per cent sugar
12 noon	.	.	0.026 ,, ,,
3 P.M.	.	.	0.077 ,, ,,
5 P.M.	.	.	0.141 ,, ,,

Despite these figures no clinical sign of hypoglycaemia had been noted and the figures were checked by repeating the chemical estimation in each case. Various combinations of insulin were tried, but it was found very difficult to avoid hypoglycaemia at some time and hyperglycaemia at other times in the twenty-four hours. After about a month of trial and adjustment it was found that 25 units of protamine insulin given twice a day were satisfactory, as shown by the following results :

10 A.M.	.	.	0.128 per cent sugar
12 noon	.	.	0.041 ,, ,,
2.30 P.M.	.	.	0.131 ,, ,,

He was finally discharged from hospital on 15 units of protamine twice daily and a 9-line diet with 100 g. of starch.

Under observation in the out-patient department it was found necessary to increase the insulin to 40 units of insoluble insulin at night and 20 units in the morning. After about seven months he was admitted to hospital comatose, cold and collapsed, and suffering from air hunger. For four days he had suffered from abdominal pain and vomiting and had taken neither food nor insulin. The blood-sugar was 0.6 per cent and the alkali reserve 13 c.cm. of carbon dioxide per 100 c.cm. of plasma. Despite treatment he died a few hours after admission.

This case illustrates almost every point in the treatment of diabetes. First, the disastrous effect of insufficient treatment is seen in the septic infection which nearly cost him his life and left him disfigured with the loss of one eye. Then the necessity to push insulin to large doses in severe cases is exemplified: without the use of insoluble insulin it is doubtful if this case could have been properly controlled. The effect of pressing the insulin dosage is then seen in the great improvement in the next curve which was taken. The recovery which ensued after he left hospital would not have led to severe hypoglycaemia if there had been reasonable co-operation on the part of the parents. The final dose on discharge from hospital for the second time compared with what was originally required, shows to what degree recovery had progressed. It is not usual to give insoluble insulin in two doses, but it was necessary in this case because the action was very delayed and a steadying effect was obtained with two doses.

The recovery was not maintained when he was at home, but this was due, as was his death, to the lack of co-operation on the part of the parents, and illustrates clearly the impossibility of treating diabetes successfully, without intelligent co-operation.

Treatment of complications: the diagnosis between hypoglycaemic coma and diabetic coma (also see pp. 245 and 246).—In the first condition the patient often appears to be asleep, the face is usually pink and healthy-looking, the skin warm and clammy or bathed in profuse perspiration. Respiration, pulse, temperature, and blood-pressure are not much altered.

Convulsions are frequent. In diabetic coma the patient looks ill, the breathing is gasping or laboured, with a smell of acetone in the breath. The skin and tongue are dry and the general appearance suggests dehydration, which is confirmed by the low tension of the eyeball on palpation. The pulse is feeble and the blood-pressure low.

If the urine contains no sugar, diabetic coma can be excluded. (This is not strictly true, as cases of diabetic coma have been reported (18) with hyperglycaemia and without sugar in the urine, but for practical purposes these extremely rare findings may be neglected.) If the urine contains much sugar and acetone, diabetic coma is present. If some sugar is found in the first catheter specimen, the possibility of hypoglycaemic coma cannot be excluded, because this urine may have been excreted before the development of hypoglycaemia. If a second catheter specimen is sugar-free, then hypoglycaemia can be diagnosed. If possible the estimation of the blood-sugar will clinch the diagnosis and the alkali reserve should be estimated as it is low in diabetic coma. It is important to remember that it is very dangerous to give insulin to a hypoglycaemic patient, but no danger is run in giving glucose to a patient with diabetic coma.

Treatment of diabetic coma.—If the patient is seen before he has become completely unconscious, 40–45 units of soluble insulin should be given intravenously immediately, followed by 30 g. of glucose and normal saline by the mouth. Doses of insulin and glucose are repeated in the rate of 1 unit of insulin to 1 g. of sugar every two hours, together with large quantities of fluid and sodium bicarbonate or sodium citrate in 3ii doses every two hours. Coma will be averted and treatment much simplified.

If the patient is comatose, the practitioner should give the child 40 units of soluble insulin intravenously and send him into hospital. Supposing that hospital treatment is not available, the practitioner must do his best using urine tests as his guide, and any scheme of treatment must be modified according to the need of the patient, using the following suggestions as a guide. After the initial dose of 40–50

units of soluble insulin has been given intravenously, a solution of normal saline should be prepared and 40 g. of glucose added to 3 pints of saline. Sodium bicarbonate should be added to this solution. It is best obtained in sterile isotonic solution in ampoules of different sizes from 50 c.cm. to 250 c.cm., the dose depending on the degree of acidosis. In our experience 250 c.cm. of sodium bicarbonate in isotonic solution will raise the alkali reserve of an adult by about 10 c.cm. CO_2 per 100 c.cm. of plasma. If sodium bicarbonate ampoules are not available a sterile solution of sodium citrate should be used. This should be given intravenously, taking about one hour. At the start of treatment a catheter should be passed and the urine tested. Thereafter it can be passed at two-hourly intervals and the insulin dose determined from the quantity of sugar and ketone bodies present and from the general condition of the patient. Soluble insulin should be given subcutaneously (in doses of about 40–50 units) at 2 hourly intervals, until the Ferric chloride test for ketone bodies is negative. More or less insulin than this may be necessary. To combat dehydration and acidosis a constant drip transfusion the composition of which has been described above may be required. After the Ferric chloride test has become negative, smaller doses of insulin should be given until the Rothera test for ketone bodies is negative also. On recovering from coma, a line diet without fat may be given with the appropriate dose of insulin for the first few days. The most important life-saving measure is to give sufficient insulin during the first few hours of coma. If the patient is in hospital, laboratory assistance greatly simplifies the treatment.

Treatment of hypoglycaemic coma in diabetes mellitus.—This condition should be prevented by watchfulness. Any patient who is taking insulin should be warned of the premonitory signs, which are usually a feeling of cold and sweating, a “sinking feeling”, and a feeling of tiredness. Two lumps of sugar should be taken at once and, if the symptoms are not completely relieved, should be repeated. Any abnormal symptom occurring at the same time on

successive days merits a blood-sugar examination to see if it is a symptom of hypoglycaemia. A great variety of hypoglycaemic symptoms have been described and mental conditions such as temporary confusion are not uncommon, while we have seen acute mania on more than one occasion. In children hypoglycaemia is not dangerous.

When the patient is seen in coma the best treatment is to give glucose intravenously. All practitioners who have the care of diabetic patients should keep ampoules of sterile glucose ready, as these are supplied containing 25 g. to 50 c.cm. of sterile water. In case of grave emergency this could be used undiluted but must then be given very slowly. It is preferable to dilute the contents with two or three times its volume of boiled water, and the injection can be given conveniently with a 20 c.cm. syringe. Recovery is usually prompt and complete but a dazed condition may persist for some hours. If glucose is not available, a stomach tube must be passed and a solution of cane-sugar given. Recovery will not be so prompt.

The treatment of hypopituitary dwarfism associated with diabetes.—White (5) prefers to treat these patients with anterior pituitary growth extract, although this may contain the diabetogenic principle because the failure of growth prevents the patient earning a living. As a result of giving growth hormone in a purposely crude extract, she finds that diabetic dwarfs require 65 units of insulin daily instead of 55 units daily for the average diabetic child. The results in growth are good.

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Hyperinsulinism

The presence of an excess of insulin, either as the result of administration in the treatment of diabetes or due to an abnormally high secretion of the islets of Langerhans, leads to a rapid lowering of glucose in the blood-stream.

Hyperinsulinism caused by therapeutic injection has been dealt with in the treatment of diabetes mellitus (p. 258). In this connection it should be mentioned that symptoms of hyperinsulinism do not always occur at the same level of blood-sugar; in the case of diabetics who have been accustomed to an abnormal amount of glucose in the circulation, hypoglycaemic symptoms may occur at levels much above the normal, especially if the diet has been too strictly limited. Again, it may happen that diabetics who ordinarily have hyperglycaemia may have attacks in which the blood-sugar level sinks to 0.047 mg. per cent or lower (1) (2). (See p. 255.)

Hypoglycaemia is not uncommon during the first few days of life and is possibly due to an imperfectly developed regulatory mechanism which creates a state of relative hyperinsulinism. A similar period of hypoglycaemia may occur in infants who are born of diabetic mothers, but in these cases there is a physiological hyperactivity or hyperplasia of the islet tissue consequent upon the stimulation caused by deficiency of the maternal secretion. Such children are of large size and over-weight and may have convulsions resembling those due to intracranial haemorrhage; they may be difficult to resuscitate or, after revival by carbon dioxide and oxygen, may sink back into coma. These patients should be examined for hypoglycaemia, and if this is found, a sugar tolerance test should be done on the mother (3) (4) (5).

Hyperinsulinism may also be caused by the formation

of adenomata or carcinomata of islet tissue, such tumours being found more frequently in the body and tail of the pancreas. A considerable number of cases are now on record in which complete recovery from hypoglycaemic attacks has followed the removal of a pancreatic adenoma.

The symptoms noticed in a mild type of case are those observed after an overdose of insulin. They are circumoral pallor, a sensation of hunger, nervousness, and irritability followed by sweating, tremor, abdominal pain, mental confusion, and vertigo, and are particularly likely to occur if the patient has been fasting overlong or has been subjected to mental or physical strain. Sometimes there may be a rapid lapse into unconsciousness accompanied by convulsions simulating epilepsy. In some patients spontaneous hyperinsulinism may cause a psychosis, often violent in form, which may occur in the early morning, late at night, or occasionally just before meal-time (6). Severe grades of hypoglycaemia are accompanied by a lowering of intra-ocular tension, a fall in blood-pressure, and a body temperature of 97° F. These signs and symptoms disappear when sugar is supplied to bring the blood back to normal, but the patient may not remember what has occurred during the attack.

The central nervous system may suffer injury from the serious disturbance in cerebral metabolism resulting from severe hypoglycaemia. The brain is largely dependent upon carbohydrate for its source of energy and the frequent reduction of the blood-sugar to a low level may cause permanent damage. It was shown by Holmes (7) that dextrose was necessary for the utilisation of oxygen by the brain and that oxygen consumption was considerably reduced by insulin hypoglycaemia. Subsequently Damshek, Myerson, and Stephenson (8) confirmed these results in human beings. They state: "In the hypoglycaemic state the uptake of oxygen by the brain (at least as measured by arteriovenous differences) appears to be materially reduced. This, together with the well-known sensitivity of the brain to diminution in its oxygen supply, may account for such phenomena as tremor, twitchings, and convulsions, the end result of the

lack of oxygen being coma." In a case reported by Malamud and Grosh (9), a woman aged 30 suffered from convulsions, psychotic manifestations, and organic dementia due to chronic hypoglycaemia caused by an islet cell adenoma. Examination of the brain showed advancing destruction of the cerebral cortex and the basal ganglia. In other cases who had severe convulsive seizures, it was found that tiny haemorrhages were scattered irregularly throughout the brain (10).

Hypoglycaemia does not occur in normal people even during starvation. It would, however, be a mistake to regard absolute hyperinsulinism as the sole cause of the condition and to neglect various other important factors which are also concerned in its production. It may occur as the result of ineffectual absorption such as takes place in coeliac disease, where low blood-sugar curves are found after oral administration of sugar, although normal curves follow intravenous injection of sugar (11). Severe damage to the liver may cause interference with storage capacity for glycogen, so that again the demand for rapidly utilisable carbohydrate cannot be met. An abnormal fixation of glycogenase to the liver proteins is apparently responsible for the low fasting level and minimal response to a test meal in Von Gierke's disease (12). There may be a failure in the normal mechanism for the liberation of sugar into the blood-stream. Thus, a deficiency in the secretion of adrenalin prevents the mobilisation of glycogen from the liver in Addison's disease, the degree of hypoglycaemia depending upon the extent to which the medulla is affected. Again, in hypothyroid states, the lack of thyroxin prevents the normal sensitisation to the action of adrenalin, so that there is an increase of the sugar tolerance, a flat blood-sugar curve, and a liability to the occurrence of attacks resembling the effects of an overdose of insulin.

The effects of hypoglycaemia due to under-activity of the anterior lobe of the pituitary gland are seen to full extent in Simmonds's disease, in which basal metabolism is very much slowed down, the sugar tolerance is increased, and death may occur in hypoglycaemic coma (13). Minor degrees of hypopituitary deficiency are also likely to be

accompanied by hypoglycaemic manifestations, so that it becomes worth while to investigate the blood-sugar curves in those cases that complain of attacks of exhaustion and "turns".

Diagnosis

Whatever the underlying pathological cause, the development of symptoms is accelerated by a need for glucose, such as occurs with physical exhaustion, prolonged mental effort, worry, or a period of fasting. The patient may provide a clue to the diagnosis by noting that he has been able to ward off or relieve the condition by taking starch or sugar. The clinical recognition of a hypoglycaemic state is rapidly confirmed by the relief afforded by giving sugar, but the establishment of the cause frequently requires prolonged investigation. Patients suffering from hyperinsulinism may have long intervals of freedom from attacks, during which the blood-sugar remains normal, so that it may be necessary to plot a sugar tolerance curve over a period of five or six hours, or even to do this while subjecting them to the circumstances which caused the attack.

All other endocrine faults must be ruled out before attributing hypoglycaemia to hyperinsulinism, for the latter is a rare condition, whereas a low blood-sugar is comparatively common. Thus, Goldzieher (14), analysing the cases of 112 patients suffering from the symptoms attendant upon a proved hypoglycaemia, found that 88 showed hypopituitarism (including 14 cases of Fröhlich's syndrome), 20 presented evidence of hypothyroidism, and 4 were hypogonadal. Of these cases, 74 were improved by organo-therapeutic measures suited to the endocrine disorder.

Treatment

As it is possible that the child of a diabetic mother may suffer from hyperinsulinism, the diabetic condition should be carefully controlled during pregnancy so as to avoid stimulation of the foetal pancreas. Such children should be assured of an adequate supply of carbohydrate during the first few days of life.

During an acute attack of hypoglycaemia, the patient is treated by the immediate administration of sugar, either as barley sugar or sweetened orange juice by mouth; or if the symptoms are severe glucose by rectal or intravenous injection. In a case of urgency the use of 3 c.cm. of 1 in 1000 adrenalin causes rapid mobilisation of sugar from the liver and brings speedy if only temporary relief. In the intervals of freedom, the patient is advised to take plenty of rest and is put on a diet which will not give a stimulus to secretion by the pancreatic islets. For this purpose, small and frequent meals are given so that there will be sufficient circulating carbohydrate to ensure normal metabolism by the brain. The quantity of protein is reduced below the normal, one meat meal in the day being allowed, and a high proportion of fat is given, partly on account of its calorie value and partly because an excess of fat in the diet inhibits insulinogenesis (15). Most of the carbohydrate, also reduced in total value, is derived from fruit and vegetables (1).

In those cases in which it is judged, from the severity of the signs and symptoms, that an adenoma is present, surgical removal offers the best hope of permanent relief.

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CHAPTER 13

FURTHER SYNDROMES OF INTEREST

Diabetes Insipidus

THIS is a symptom complex characterised by the persistent passage of large amounts of urine of low specific gravity free from sugar and albumin. Cushing's (1) conclusions on the cause of diabetes insipidus are as follows :

“ The evidence at hand seems reasonably convincing that the disorder can be produced by nuclear degeneration from disease, by surgical injuries of the supra-optic region in operations about the chiasm, by the interruptions of the nerve tracts in course, whether from tubercular tumours or punctures, by the experimental placement of a clip on the infundibulum and probably also (could this be accomplished) by complete removal of the epithelial investment which apparently elaborates the posterior lobe secretion—all of which indicates a diencephalo-hypophyseal mechanism which can be broken at any one of three points—nucleus, fibre tract, and pars intermedia et tubercularis.”

This break in the chain wherever it occurs probably produces the syndrome by interference with reabsorption of water in the kidney tubules the control of which is one of the functions of posterior pituitary secretion, and the majority of cases are controlled by giving posterior pituitary extract. There is, however, a group of cases which is quite resistant to treatment, and Biggart (6) has shown that these pituitary resistant cases are the result of cerebral injury. Recently (7) he has reported two further cases with autopsy, from which he draws the following conclusions : “ That in the human subject damage to the nuclei of the tuber cinereum with or without concomitant damage to the supra-optic-

hypophyseal system, results in a form of diabetes insipidus which is not controlled by the antidiuretic factor". No explanation is given but it is pointed out that any hypothesis must explain this mechanism, and these cases constitute a barrier to the idea that the syndrome is purely an endocrine deficiency dependent entirely on the secretory changes brought about by lesions of the supra-optic-hypophyseal system.

There are two groups of cases of diabetes insipidus.

In the primary group no organic lesion can be found and a hereditary factor is often present. The onset occurs usually in youth or childhood and is slow and insidious.

In the secondary group there is injury to the structures of the neuro-hypophyseal mechanism by trauma, tumour, or infection, possibly the most common being syphilitic basal meningitis.

Primary Group

Weil (2) has described a family in which of ninety-one members of four generations no less than twenty-three had persistent polyuria. In one of his cases the parents could tell by the sixth month whether the child was going to be affected by the disease. Other authors (3) have reported additional examples and give the following account of symptoms. Polyuria is never present at birth but may develop at an early age. The signs are dissatisfaction with the breast milk, restlessness, and wakefulness at night which is relieved by drinking. At about the age of 2 years, paralleling the transference of the function of regulation of water exchange from the skin and gastro-intestinal tract to the kidneys, the symptoms associated with the syndrome of diabetes insipidus appear. These are nocturnal and diurnal polyuria, polydipsia, and enuresis which may persist to adult life.

We have seen a number of adult cases in which no evidence of any organic lesion could be found, but only one child falls into this group. No hereditary influence was present in any of them.

CASE No. 134.—A girl of $4\frac{1}{2}$ years. The family history was

normal. At the age of 12 months she started to drink excessively and this persisted. Recently she had drunk her own urine and that of her small brother. She was thin and undersized, being 2 inches below the minimum height, and the appetite was poor. The intelligence was about the normal level for the age and no signs of an intracranial lesion could be found. On admission to hospital the condition varied considerably; at times there was little craving for fluid, at other times she drank the water from the flower vases in the ward. Neither treatment with posterior pituitary powder intranasally nor with pituitrin by injection made any difference to the condition. After being under observation for two years without material change the family left the district and further history is not available. This patient has been classed in the primary group, but there were two points which may indicate that pituitary disorder lay behind the symptoms, namely—she had a fine wrinkled skin, and a younger brother whom we examined at the age of 3 showed an underdevelopment of the scrotum with palpable though imperfectly descended testes, signs which are attributable to hypopituitarism.

The Secondary Group

All our cases except one have shown this symptom in association with childhood pituitary obesity without evidence of pituitary tumour. The symptoms in these patients were not as a rule very severe, and quickly and permanently cleared up when treatment for this syndrome together with some posterior pituitary preparation was given. Some of them also showed excessive desire for food. The one patient who did not show signs of childhood pituitary obesity is worth quoting because of the severity of the symptoms, the prolonged period that he has been under observation, and the degree of recovery that has occurred.

CASE No. 63.—Plate No. 21. A boy aged 8 years, the sixth of ten normal brothers and sisters. The parents were healthy. Apart from childish ailments and pneumonia two years previously, he had been quite well until two months before attending hospital when he began to suffer from severe thirst, causing him to drink eight pints a day. He had always been small, very shy and rather dull at school, but in the last two months had become very bad-tempered.

On examination, he was a puny undersized boy with a sallow

complexion. Both testes were very small and could be felt in the inguinal canal. He passed up to twelve pints of urine per day, of low specific gravity but otherwise normal. No evidence of gross pituitary lesion was found nor has any appeared in the succeeding seven years of observation. The case was diagnosed as anterior lobe hypopituitarism, with a recent superadded disorder of the hypothalamic-hypophyseal mechanism.

Treatment and subsequent course.—The patient was given posterior pituitary powder intranasally and the condition was immediately controlled. Two doses in the twenty-four hours were sufficient, for the effect of one dose lasted exactly twelve hours, and if the next dose were delayed he started to drink and pass excessive quantities of urine immediately. At first the dose of powder was 1 gr. per twenty-four hours given in two doses. By the time he was 10 years old one dose in the twenty-four hours was sufficient to keep him normal. At 11 years only a quarter of the original dose was required. If a dose were omitted he would go 4–5 hours before symptoms developed. Nervousness and shyness had diminished and his school work improved. The interest of observing the gradual improvement in the diabetes insipidus had taken our attention from his general development, for at the age of 12 years the height was 3 in. and the weight 11 lb. below the minimum normal and the genital organs were still small although the right testis had descended. By the age of 13 years he had become good at school, being second out of forty boys, but as general and genital development was still below normal, anterior pituitary powder was given twice daily, separately from the posterior pituitary powder. At the age of 14 years he was without posterior powder for one week, only moderate thirst was experienced and he passed urine every three hours instead of every twenty minutes as had been the case in the past when powder had been omitted. At the age of 15 years both testes had descended, but pubic and axillary hair was absent and the voice had not broken, the height was 6 in. and the weight 19 lb. below the minimum normal. The original diagnosis of anterior hypopituitarism had been justified by events, but unfortunately preoccupation with the symptoms of diabetes insipidus had caused us to neglect the child's general development and he has not been given in the last few years the energetic treatment which he should have had.

Diagnosis

In severe cases the diagnosis is obvious; absence of hyperglycaemia and glycosuria distinguish the condition

from diabetes mellitus, the absence of albumin and casts in the urine from chronic nephritis. The Wassermann reaction of the blood serum should be tested to exclude syphilis, and examination of the central nervous system including the visual fields and stereo-radiograph of the skull should be made to exclude a tumour of the pituitary or its neighbourhood.

Treatment

If syphilitic, treatment for that disease must be instituted ; if evidence of a local tumour is found, direct attack upon it by surgery or deep therapy must be considered. In the majority either no organic lesion can be found at all, or else evidence of functional pituitary disorder is present and in all these cases posterior pituitary extract usually controls the condition. In the first place we always give posterior pituitary powder by nasal insufflation, as described on p. 93. The amount and the number of doses required each day has to be determined for each patient. We have been able to control in this way all the patients in whom the symptom was associated with childhood pituitary obesity. We have only seen two other children with the condition, both described above (Nos. 63 and 134), in one of whom it was easily controlled by intranasal pituitary powder ; in the other all pituitary preparations were equally ineffective. As a matter of interest it may be mentioned that about half our adult cases, none of whom are associated with any obvious lesion, are satisfactorily controlled by pituitary powder. If treatment with powder fails, then the gland must be given by subcutaneous injection, the dose depending on the severity of the symptoms, $\frac{1}{2}$ to 1 c.cm. of Burroughs Wellcome's Pituitrin, two to four times a day, being usually sufficient. Apart from the discomfort of injection, this method of giving pituitary has the disadvantage of often producing general reactions, such as pallor of the face and syncope and intestinal spasm with abdominal pain in some patients.

The Laurence-Moon-Biedl Syndrome

This is a rare congenital condition of which a careful review has been written by Reilly and Lissner (4), who analyse seventy-three cases from the literature and add four more of their own. They give six cardinal symptoms: (1) obesity, (2) genital dystrophy, (3) retinitis pigmentosa, (4) mental deficiency, (5) polydactylism, (6) familial occurrence. In only twenty-five of the seventy-three cases was the complete syndrome present, but familial occurrence is necessary if the diagnosis is to be made in the absence of any of the other cardinal points. The pathology of the condition is doubtful; some authors favour a pituitary origin owing to the presence of obesity and genital dystrophy, others consider that a cerebral developmental defect is present, but further post-mortem studies are required before a definite hypothesis can be formulated. The skeletal abnormalities, polydactylism and syndactylism and the familial occurrence, clearly point to a genetic influence. Anderson (8) recently reported a case showing obesity, blindness, genital hypoplasia, polydactylism, and possible mental deficiency. At autopsy an increase in the basophilic elements of the anterior pituitary and a colloid goitre with hypothyroidism were found. The author notes that three out of six post-mortem examinations reported in this syndrome have shown some abnormality of the pituitary gland. Partial examples of this syndrome occur and should be studied, for they may throw light on the pathology of the full syndrome by indicating the relation with other conditions. We have seen several such cases of which the following is one example.

He was a man of 32 years who gave a history that he had always been fat and suffered from headache and myopia. Recently the sight of the right eye had become suddenly worse.

On examination, he was 74 in. high, weighed 238 lb., and showed a pituitary distribution of obesity. The genital organs were very small and there was a feminine distribution of pubic hair. The red complexion completed the resemblance to the childhood pituitary obesity type; the neck was full and the thyroid gland could be palpated.

The ophthalmic surgeon, Mr. Cashell, reported that a condition similar to retinitis pigmentosa due to a degeneration of the choroid was present with night blindness. Mental deficiency was absent and the family history was not very significant, the father being obese and myopic and the mother's father becoming blind late in life, but the association of retinitis pigmentosa with a pituitary distribution of fat and genital dystrophy is of interest.

Treatment

One could scarcely expect much improvement from treatment in this condition and in many of the reported cases it was not attempted. However, it is worth while reducing the weight and many authors have noted improvement with thyroid, pituitary, and ovarian extracts. Reilly and Lissner (4) report improvement in two of their four patients who were given thyroid and pituitary extract. One showed definite mental and visual improvement, the other became more alert, and they both lost weight. Our patient reported above was treated with injections of acetylcholine followed by whole pituitary injections. The vision improved but it is not possible to say to which treatment this should be ascribed.

Lipodystrophia Progressiva

(*Synonym* : Barraques-Simons disease)

This is a rare disease which may occur at any age but usually starts in childhood and is characterised by progressive symmetrical loss of subcutaneous fat in the face, neck, thorax, and abdomen to the level of the iliac crests, below which it never extends, although it may in some cases be limited to a portion of that area. The lower part of the body is either normal or shows an excess of fat. The onset usually occurs between the age of 5 and 8 years in a female child and the following case shows the typical features :

CASE No. 147.—Plate No. 48. A girl of 10½ years. The mother is stout, with some development of moustache and beard ;

the father is normal and there are no other children. The patient weighed 7 lb. at birth and developed normally until 7 years old, when a remarkable change took place. Within one month the face and the upper part of the body became thin while the lower part remained normally developed; her features had previously been round, resembling the mother, but afterwards all resemblance disappeared, the lack of subcutaneous tissue giving her a drawn and aged appearance. This rapid change is confirmed by snapshots taken before and after the occurrence. She remained in the same condition until about $9\frac{1}{2}$ years old, when she began to put on weight below the umbilicus.

On examination, the patient showed a remarkable difference between the upper and lower parts of the body; below she was markedly obese with a pot-belly and fat thighs, the ribs were plainly visible above, the breasts ill-developed, and the pinched face clearly showed the bony prominences, resembling in that respect the appearance of patients with Simmonds's disease or with primary hypogonadism. The face was not that of a child of 10 years but might have belonged to an adult between 30 and 35 years of age. The intelligence was normal and the child made no complaint; there were no other physical signs and the visual fields were normal. A stereo-radiograph of the skull showed a normal pituitary fossa and the development of the epiphyses corresponded to her age; on the other hand the development of the teeth* was prematurely advanced by three years. She has been under observation for two and a half years. The measurements are as follows:

Case No. 147	Age $10\frac{1}{2}$ Years	Normal for $10\frac{1}{2}$ Years	Age 11 Years	Normal for 11 Years	Age 12 Years	Normal for 12 Years	Age $12\frac{1}{2}$ Years	Normal for $12\frac{1}{2}$ Years
Weight (lb.)	91	59-75	100	64-81	109	71-90	111	74-96
Height (in.)	54	52-56	55	53-57	57	55-59	57-75	56-61

From these figures it will be seen that the height is about the mean normal, while the weight is excessive; at the age of $10\frac{1}{2}$ years it was 32 lb. above the maximum normal and at the age of $12\frac{1}{2}$ years it is still 37 lb. above the maximum normal, figures that are striking considering the emaciation of the upper part of the body. It is, however, satisfying to note that there has been a gain of only 2 lb. during the last six months. As indicated by these figures, the condition has changed very little during the period of observation. At the age of 12 years the breasts began to develop, pubic hair appeared, and four months later menstruation started; at the age of $12\frac{1}{2}$ years the upper part of the body

presented a more normal appearance owing to the breast development, but the face and hands remained very thin and aged.

The patient was given anterior and posterior pituitary powder for one year and small doses of fresh thyroid gland for the succeeding year. Treatment was given rather with the idea of keeping her under observation than with any hope of therapeutic success.

There are several points of interest in this case. Although we have not examined the mother, her appearance suggests that she suffers from an endocrine dysfunction. The mode of onset of the condition indicates unmistakably a sudden glandular disturbance, akin to the development of Simmonds's disease. A similar loss of subcutaneous tissue, although not limited to one area, occurs in Simmonds's disease, progeria, and primary hypogonadism, and in well-marked cases of growth defect (see Case No. 61, p. 105). It remains a task for the future to construct a hypothesis to account for this condition but a good review has been contributed by Roger (5). This author points out that to the original picture of the disease others have added vaso-motor disturbance, nervous symptoms such as anxiety states, polyuria and glycosuria and bony deformities. It is of interest to note that the distribution of obesity in these patients is the opposite to that found in Cushing's disease, but it is difficult to construct a hypothesis primarily involving the pituitary because no experiments on the gland have reproduced the condition nor does administration of pituitary gland preparations influence it. He also considers the question of the involvement of the central nervous system and mentions the theory that a congenital or acquired defect in the segmental trophic centres of the spinal cord or in the sympathetic centres might be an explanation of the metamerie distribution, and mentions that a case has been described of encephalitic origin in which striatal change was found.

The Occurrence of “ Crisis ” in Endocrine Disorder

By the term “ crisis ” is meant a sudden failure of endocrine function which leads immediately to dramatic sequelae.

Special emphasis should be put upon the conception because it may suggest the endocrine origin of conditions which might be attributed to other causes. The best-known endocrine crisis is associated with hyperthyroidism, and in the course of that disease the patient's condition may suddenly deteriorate either spontaneously or following some shock. The rate of the heart mounts, the basal metabolic rate soars, sweating, insomnia, and mental distress may precede a fatal termination. A crisis of this kind was a serious danger following thyroidectomy before pre-medication with iodine became a routine precaution. Adrenal disease affords the next most common example of crisis in endocrine function and this has been fully described on p. 160. It is most usually found in association with Addison's disease but occurs in other conditions, and we have seen an acute adrenal failure in a previously healthy woman after childbirth. Acute adrenal haemorrhage in the new-born affords another example of endocrine crisis. Operation for removal of an adrenal cortical tumour may precipitate an adrenal crisis through the sudden deprivation of hormone from the tumour cells. This may now be prevented by the use of a potent cortical extract or corticosterone. It is less commonly recognised that diabetes mellitus may start as a sudden event, and we have seen patients admitted to hospital with acute diabetic symptoms presumably due to a sudden failure of the islet tissue of the pancreas whose urine has been known to be normal a few days before.

The occurrence of a crisis of pituitary function is not nearly so frequently recognised except in association with acute conditions such as Simmonds's disease, yet it does occur. We have already noted that childhood pituitary obesity often either starts suddenly or an exacerbation occurs spontaneously or following an acute infection, which must indicate a recent failure of glandular function. A case of diabetes insipidus (with a similar acute onset) was quoted above, and we have seen an adult patient with diabetes insipidus in whom the symptoms started in the same way. The sudden development of hunger and thirst which has been noted in several of the childhood pituitary obesity cases raises

the question whether suddenly developing anorexia may not also be an endocrine symptom. In that case another point of contact would be made between anorexia nervosa and pituitary function. We have seen other cases that suggest how closely endocrine function and appetite are bound up. For example, a woman complained of ravenous hunger and wasting but there were no physical signs of organic disease except emaciation. When investigated as a suspected diabetic the blood chemistry was normal and there was no evidence of hyperthyroidism. For a time her appetite remained excessive, and she continued to lose weight, but with prolonged rest in hospital the symptoms gradually abated and she was discharged in a fair state of health. Observation for several years has not thrown any further light on the condition and we can only suspect that some endocrine crisis occurred the nature of which remains uncertain. In obscure cases such as these the conception of endocrine crisis forms a starting-point in considering the disease. The patient with lipodystrophy reported above is another example of a very obscure condition, in which the mode of onset strongly suggests a sudden endocrine failure. When speaking of crisis in relation to the pituitary gland, it is probable that the whole hypothalamic-hypophyseal mechanism is involved, and it may well be that a hypothalamic change initiates the glandular failure, for in childhood pituitary obesity and diabetes insipidus, for example, there is certainly an underlying hypothalamic dysfunction.

REFERENCES

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- (4) Reilly and Lisser, *Endocrinology*, 16 : 337, 1932.
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CHAPTER 14

MENTAL SYMPTOMS IN ENDOCRINE DISORDER IN CHILDREN

THE consideration of mental symptoms in relation to endocrine dysfunction opens up vast fields for speculation, but we propose to restrict our remarks to personal experience.

We have dealt at considerable length with the physical development of the child, and here we are considering the development of the personality and the intellect, which proceed at the same time. Now, of what does the character of an individual consist? To follow Macdougall (1), the native basis of the mind is built up of certain innate predispositions and instincts with their impulses and tendencies and the resultant of these constitutes the disposition, so that for example we speak of an irascible or timid disposition. Temperament is the sum of these innate characteristics together with the effect which is exerted on the nervous system and through that on mental processes, by the bodily organs. Probably every organ in the body exerts its influence upon mental life in two ways: firstly, by a chemical or hormonal influence, and secondly, by the constant flow of sensation through the afferent nerves maintaining the coenaesthesia of the nervous system on which the general tone of mental life depends. The character or personality of the individual is the sum of tendencies which have been acquired during development built up on the basis of disposition and temperament. Disposition and temperament are mainly inborn, whereas character depends largely on efforts made during development. We can see that the personality of the individual may be affected by endocrine influence in two ways: firstly, by a direct physiologic

influence on temperament, and secondly, by an indirect mental effect caused by the reaction of the individual to the physical disability caused by the endocrine dysfunction. In some cases it is difficult to say where one influence starts or ends but a few points stand out sufficiently clearly to be of value to the clinician.

We will take intellectual development first, as that is the easier to estimate. It proceeds at the same time as the development of the personality but at a faster rate, since it is normally complete at the age of 14-15 years. Hypothyroid cases show slow and imperfect mental development, probably in part due to lack of differentiation of nervous tissue and in part due to slowing of metabolism. All degrees of impairment of intellect are found and the result of treatment depends not only on these factors, but also upon the innate intellectual capacity of the child, a point which is sometimes overlooked. For if the child is naturally dull, then an added thyroid dysfunction will produce a degree of disability for which no treatment will avail; but if for hereditary reasons he would probably have been of superior intelligence, then thyroid treatment might bring him up to normal development.

Excess or defect of pituitary or gonadal hormones is not associated with a particular degree of intelligence, although that statement may perhaps admit of one qualification. Engelbach (2) amongst others has noticed that patients with childhood pituitary obesity are often mentally precocious and in our series an unusual number appear to be of superior intelligence, but dull patients are also found and we have not examined a sufficient number to state categorically that their average intelligence is above normal, although the impression remains that such is the case. See p. 77.

We will now consider the effect of hormonal influence upon the emotional development of the individual, and the general effect which is exerted on the temperament will be considered first. On the basis of disposition and temperament the character is gradually developed throughout childhood by external influences such as parental instruction and contact with other children. Primitive instincts and

tendencies are modified and controlled, enduring emotional sentiments such as love of one's home and parents come to form part of the structure of the mind, and as the intelligence matures so the personality develops into the well-balanced individual who can play a normal part in his environment. Now this proper balance is likely to be upset where an endocrine dysfunction is having an abnormal effect upon the patient's temperament, for the instincts which the developing individual has to learn to direct and control are intimately associated with the endocrine glands. To state this as a theoretical fact is easy, but to prove the effect of endocrine dysfunction on emotional development is very difficult, for there are usually many other factors to confuse the issue regarding endocrine influence. But outstanding examples are sometimes seen in which direct endocrine influence on emotions is clear. If the description of the small boy No. 131 (p. 126) is read again, the abnormal effect of the endocrine disorder on the child's temperament will be apparent. The symptoms are to be ascribed in all probability to a stimulus from the hypothalamus acting on the anterior pituitary lobe with a consequent excitation of all bodily processes shown by excessive growth and activity. This question of activity is of interest; hypothyroid children are slow and their general activity is much reduced but when over-dosed with thyroid gland they become restless and irritable. The activity of the little boy No. 131 may have been due to excess of thyrotropic hormone of the anterior pituitary lobe, or perhaps it was an expression of general hormone over-production, of which the thyroid activity formed a part. The premature sexual stimulation in *pubertas praecox* does not always result in increased activity, for some of these patients become shy and seclusive, but perhaps that is a mental reaction to the abnormal development. In the chapter on hyperpituitarism we have described the child who a few years before puberty grows very rapidly and shows at the same time the sexual and emotional development of the adult. Such a patient (No. 80) is described on p. 120, and the activity of all kinds which she displayed was again attributed to over-production

of hormones. It is of interest to note that most of these cases of hyperpituitarism show an enlarged thyroid, doubtless an expression of the increase in metabolism, although in some cases instead of excessive activity a general emotional instability results.

If we consider the types of endocrine disorders in which secretion is deficient a different state of affairs is found; instead of energy and activity we find lassitude and inactivity. This refers to hypothyroid, hypopituitary, and hypogonadal cases, and they all suffer during development in consequence. As the normal child develops he becomes more confident, breaks away from his mother's influence, holds his own amongst his fellows, at puberty becomes more aggressive and begins to take an interest in the opposite sex. This development is often incomplete in all these groups of patients, but naturally every variety of change is found, for innate and psychological factors play their part. For example, patient No. 72 suffered from a very severe growth deficiency and complete sexual underdevelopment, yet she remained mentally balanced. Her main complaint was of extreme lack of energy, which cleared up entirely with treatment. On the other hand, patient No. 51, a boy of 16 years suffering from the same condition, was lacking in confidence and easily imposed upon by his younger brothers. In general this is characteristic of children with hypopituitarism (growth hormone) deficiency; they are submissive in type and lack power of aggression. We have noticed treatment cause immediate improvement in these respects and also in school work, not because of any direct effect upon the intelligence, which is usually normal, but because lack of drive and initiative had previously crippled their activities. Patient No. 51 went up two forms at school after treatment had begun to take effect. The personality of some of the children in this group remains so undeveloped that they cannot take their place in the world with any success. Case No. 50 described on p. 109 is an example.

In childhood pituitary obesity a somewhat similar state of affairs is found but not to so great a degree. The majority

of the children are bright, loquacious, and active and can hold their own with their fellows despite physical disadvantages, but they are submissive in type rather than aggressive and may remain unnaturally dependent. They differ of course from the patients just described in usually not having growth deficiency, and perhaps that may account for the mental difference. At puberty both these groups may suffer from sexual disability, so that there is no distinction in that respect. At times these children complain of headache and somnolence, perhaps associated with increased hunger and thirst, their school work suffers severely and the school teacher reports an inability to concentrate. Treatment usually produces immediate improvement, but we have seen patients in whom such a condition has become chronic.

The primary hypogonadal group shows the most severe mental symptoms. Lack of gonadal secretion has always been associated with psychical change. Eunuchs have proverbially a childish, timid personality which is again noted in a recent study (3) of the subject. We can emphasise this from the study of our patients: emotionally they remain undeveloped, dependent on their parents, lacking in confidence though not always in ability, and prone to develop severe neurosis of the neurasthenic type. They differ from the typical childhood pituitary obesity patient who is quick and energetic, and are more severely incapacitated than the growth defect cases. This is the group in which migraine particularly but also other forms of headache, bilious attacks, and habit spasms are very frequent. The childhood pituitary obesity group are said to suffer from the pituitary type of headache, i.e. headache severe and persistent in the frontal region and at the base of the nose, but in our series headache was an infrequent complaint: in the hypogonadal group it is almost invariable. In the chapter on primary hypogonadism the nervous symptoms of severe patients were mentioned. Patient No. A1, p. 174, affords an example of a completely undeveloped personality which one must associate with her undeveloped sexual system. This woman has a rather fatuous, childish manner, is easily pleased,

suggestible, and confiding, and as dependent on her mother as a child of 10 ; yet she has the ability to earn her living as a dressmaker and must therefore possess reasonable power of application. The gastro-intestinal symptoms associated with visceroptosis, the circulatory symptoms associated with tachycardia and blue and cold extremities, colour the innumerable complaints of these patients and lead the doctor to make a diagnosis of chronic neurasthenia without attaching due weight to evidence of endocrine dysfunction. The probability that this constitution lies behind some of the cases of anorexia nervosa has already been discussed on p. 201.

It is often difficult to distinguish between the symptoms which have been briefly described above and those which are a direct mental reaction to the disability from which the child is suffering. The patients suffering from childhood pituitary obesity usually adapt themselves well to circumstances despite the considerable handicap which increased weight imposes. Their capacity for sports is diminished both by obesity and by a natural clumsiness of hands and feet from which many of them suffer. In consequence some of the children become extremely self-conscious and may develop a shy, seclusive attitude or one of aggression or self-assertion. As puberty approaches these reactions may be accentuated by the failure in development of sexual organs and function.

Now exactly the same reactions may be seen in the patients suffering from hypopituitarism or primary hypogonadism, but these types of patients do not usually possess the same energy and capacity as the pituitary obesity patients and are therefore not so likely to develop an aggressive form of compensation. Both types of patient, but particularly those suffering from primary hypogonadism, are liable to develop the multiple symptoms and complaints called neurasthenia. It must of course be understood that the psychological reaction which a patient may develop depends not only on the degree of endocrine disability but on the innate and acquired characteristics of his own personality and the factors in his environment. Enough has been said to indicate

that where behaviour problems are present in young people the possibility of an endocrine factor should be remembered.

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- (3) Osman and Schuhree, *Hyg. Ment.*, 30:33, 1936.

SEX HORMONES
STANDARDISED COMMERCIAL PREPARATIONS

SEX HORMONES

STANDARDISED COMMERCIAL PREPARATIONS

arranged in alphabetical order

i.u. = international unit i.b.u. = international benzoate unit
 1.0 mgm. oestrone is equivalent to 10,000 i.u.; 1.0 mgm. oestradiol benzoate is equivalent
 to 10,000 i.b.u.; 1 mgm. progesterone is equivalent to 1 i.u.

Name of Preparation	Description	Maker
ANDROSTERONE AMPOULES		
ANDROFORT	1 mil contains 2 i.u.	Richter
ERUGON	1 mil contains 2 comb-growth units	Bayer
PROVIRON	1 mil contains 5 mgm. of androsterone benzoate	Schering
ANTERIOR PITUITARY EXTRACT FROM THE GLAND		
AMBINON "A"	Each ampoule contains 100 to 300 guinea-pig units thyrotrophic hormone, 50 rat units pituitary gonadotrophic hormone with 100 rat units gonadotrophic hormone of pregnancy	Organon
AMBINON "B"	Each ampoule contains 100 to 300 guinea-pig units thyrotrophic hormone with 50 units gonadotrophic hormone	Organon
ANTOXYLIN	1 mil contains 2 gr. desiccated gland	Oxo
BIOGLAN NATURAL GONADOTROPHIC HORMONE	Each ampoule contains 100 or 500 rat units natural gonadotrophic hormone, with solvent	Bioglan
GONADOTRAPHON ..	Each ampoule contains 100 or 500 rat units from 25 or 125 gr. of fresh anterior pituitary, with solvent	Paines & Byrne
LUTEOANTIN	Each suppository contains 100 rat units. Each ampoule contains 100 or 400 rat units	Richter
POLYANSYN	Each 5 mil vial contains total hormone of anterior pituitary	Armour
PRELOBAN	Each ampoule contains 25 maturation units, with solvent	Bayer
THYROGAN	Each ampoule contains 50 guinea-pig weight units, with ampoules of solvent	B.D.H.
GLANOID THYROTROPHIC FACTOR	1 mil contains 50 Collip units	Armour
THYROTROPIN	Each ampoule contains 100 guinea-pig units of hormone from approx. 1 gm. fresh anterior pituitary, with solvent	Paines & Byrne
ANTERIOR PITUITARY EXTRACT TABLETS AND CAPSULES		
GONADOTRAPHON TABLETS	Each tablet contains 100 or 200 rat units from fresh anterior pituitary	Paines & Byrne
GONADOTRAPHON CAPSULES	Each capsule contains 500 rat units	Paines & Byrne
HOMHORMON	Each tablet contains 200 rat units	Camden
PITEXAN CAPSULES ..	Each capsule contains total hormones of anterior pituitary	Paines & Byrne
PREGNYL TABLETS ..	Each tablet contains 100 or 500 rat units	Organon
CORPUS LUTEUM HORMONE AMPOULES		
GESTONE	1 mil contains 1, 2, 5 or 10 mgm.	Paines & Byrne
GLANDUCORPIN	1 mil contains 2 or 5 mgm.	Richter
LIPO LUTIN	1 mil contains 1 or 2 mgm.	Parke Davis
LUTEOMENSIN	1 mil contains 0.5 mgm.	Paines & Byrne
LUTEOSTAB	1 mil contains 2 or 5 mgm.	Boots
LUTOCYCLIN	1 mil contains 2, 5 or 10 mgm.	Ciba
LUTOGYL	1 mil contains 2, 5 or 10 mgm.	Roussel
PROGESTERONE	1 mil contains 1, 2 or 5 mgm.	Oxo
PROGESTIN	1 mil contains 1, 2, 5 or 10 mgm. Also in 5 and 10 mil vials	Organon
PROGESTIN	1 mil contains 1, 2 or 5 mgm.	B.D.H.
PROGESTONE	1 mil contains 0.04, 0.2, 0.5, 1 or 5 mgm.	Carnerick
PROLUTON	1 mil contains 2, 5 or 10 mgm.	Schering

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Name of Preparation	Description	Maker
CORPUS LUTEUM HORMONE TABLETS		
GESTONE-ORAL	Each tablet contains 5 mgm.	Paines & Byrne
LUTEOMENSIN	Each tablet contains 1/5 or 1/3 gr. extract of corpus luteum	Paines & Byrne
GLANOID	Each tablet contains 1/2 gr., 1, 2 or 5 grs. extract of corpus luteum	Armour
LUTOCYCLIN	Each tablet contains 5 or 10 mgm. anhydro-hydroxy-progesterone	Ciba
LUTOGYL	Each tablet contains 5 or 10 mgm. synthetic progesterone	Roussel
PROGESTORAL	Each tablet contains 5 or 10 mgm. anhydro-hydroxy-progesterone	Organon
PROLUTON C	Each tablet contains 5 or 10 mgm. anhydro-hydroxy-progesterone	Schering
GONADOTROPHIC HORMONE FROM PREGNANT MARES' SERUM		
ANTOSTAB	Each ampoule contains 100 mouse units (equivalent to 200 rat vaginal cornification units), with solvent	Boots
GESTYL	Each ampoule contains 200 or 400 i.u.	Organon
GONADOTROPHIC FACTOR	5 mil vials containing 300 Collip units per mil	Armour
GONADYL	Each ampoule contains 40 Evans's units (400 mouse units), with solvent	Roussel
LUTEOANTIN	Each ampoule contains 100 or 400 rat units, with solvent	Richter
SEROGAN	Each ampoule contains 200 or 1000 i.u., together with ampoules of solvent	B.D.H.
GONADOTROPHIC HORMONE FROM PREGNANCY URINE		
ANTREGONE	Each ampoule contains 166 i.u.	Abbott
ANTUITRIN "S"	10 mil vials, 100 i.u. per mil, and 5 mil vials, 500 i.u. per mil	Parke Davis
FOLLUTEIN	Each vial contains 500, 1000 or 5000 rat units	Squibb
GLANDUANTIN	Each ampoule contains about 100 rat units, with solvent	Richter
GONADOTRAPHON S	Each ampoule contains 100 or 500 rat units, with solvent	Paines & Byrne
GONAN	Each ampoule contains 100 or 500 i.u., with solvent	B.D.H.
HOMHORMON	Each ampoule contains 100 rat units, with solvent	Camden
PHYSOSTAB	Each ampoule contains 100 mouse units (equivalent to 1500 rat vaginal cornification units), with solvent	Boots
PREGNYL	Each ampoule contains 30, 100, 500 or 1500 i.u., with solvent	Organon
PROLAN	Each ampoule contains 100 or 2000 i.u., with solvent	Bayer
HEXOESTROL AMPOULES		
HEXOESTROL	1 mil contains 1 or 5 mgm.	B.D.H.
HEXOESTROL	1 mil contains 1 or 5 mgm.	B. Wellcome
SYNTHOVO	1 mil contains 1 or 5 mgm.	Boots
HEXOESTROL TABLETS		
HEXOESTROL	Each tablet contains 0.5, 1 or 5 mgm.	B.D.H.
HEXOESTROL	Each tablet contains 1 or 5 mgm.	B. Wellcome
HEXOESTROL—ORGANON	Each tablet contains 0.1, 0.5, 1 or 5 mgm.	Organon
SYNTHOVO	Each tablet contains 1 or 5 mgm.	Boots
LACTOGENIC HORMONE OF THE ANTERIOR PITUITARY		
PHYSOLACTIN	1 mil contains not less than 60 Riddle-Bates units	Glaxo
PROLACTIN	1 mil contains 100 Prolactin units (Riddle)	Armour
PROLACTIN	1 mil contains 60 Riddle units	A. & H.

Name of Preparation	Description	Maker
OESTRADIOL AMPOULES (usually Benzoate)		
BENZO-GYNOESTRYL	1 mil contains 1000, 10,000 or 50,000 i.b.u.	Roussel
BENZTRONE	1 mil contains 1000, 10,000, 20,000 or 50,000 i.b.u.	Paines & Byrne
DI-MENFORMON	1 mil contains 10,000 or 50,000 i.b.u. Also 5 and 10 mil vials	Organon
OESTRIN	1 mil contains 1000, 10,000, 20,000 or 50,000 i.b.u.	Oxo
OESTROFORM	1 mil contains 1000, 10,000, 20,000 or 50,000 i.b.u.	B.D.H.
OESTRONE	1 mil contains 1000 or 10,000 i.b.u.	Hewlett
OVOCYCLIN P	1 mil contains 10,000 or 50,000 i.b.u. "dipropionate units"	Ciba
OVOSTAB	1 mil contains 2000, 10,000 or 50,000 i.b.u.	Boots
PROGYNON D.P.	1 mil contains 20,000 i.b.u. oestradiol dipropionate	Schering
PROGYNON B. OLEOSUM	1 mil contains 10,000 or 50,000 i.b.u.	Schering
UNDEN	1 mil contains 10,000 or 50,000 i.b.u. Also 10 mil vials containing 10,000 i.b.u. in 1 mil	Bayer
OESTRADIOL TABLETS		
GYNOESTRYL	Each tablet contains 0.025 mgm.	Roussel
GYNOESTRYL S	Each tablet contains 0.2 mgm.	Roussel
OESTROFORM	Each tablet contains 1000, 5000 or 10,000 i.u.	B.D.H.
OVOCYCLIN	Each tablet contains 0.04 mgm. or 0.2 mgm.	Ciba
OESTRADIOL AND BENZOATE PREPARATIONS		
DI-MENFORMON OINTMENT	1 gm. contains 20,000 i.b.u. oestradiol benzoate	Organon
ECTO-GYNOESTRYL OINTMENT	25 gm. contains 2.5 mg. oestradiol	Roussel
ECTO-GYNOESTRYL SOLUTION	10 mil contains 5 mgm. oestradiol	Roussel
GYNOESTRYL SOLUTION FOR ORAL USE	10 mil contains 1 mgm. oestradiol	Roussel
OESTROFORM PESSARIES	Each pessary contains 1000 i.u.	B.D.H.
OVOCYCLIN OINTMENT ..	25 gm. contains 2.5 mgm. oestradiol	Ciba
PROGYNON OINTMENT ..	25 gm. contains 2.5 mgm. oestradiol in neutral base	Schering
PROGYNON VAGINAL CAPSULES	Each capsule contains 0.25 mgm. oestradiol	Schering
PROGYNON VAGINAL SUPPOSITORIES	Each suppository contains 0.36 mgm. oestradiol	Schering
SEDO-GYNOESTRYL ..	1 mil contains 1000 i.u. oestradiol with 0.5 gm. NaBr, and 0.02 gm. Ext. Hyosey.	Roussel
OESTRIOL		
EMMENOPLEX	1 mil contains 30 (Wistar) units oestriol monoglycuronide	Glaxo
THEEOL CAPSULES ..	Each capsule contains 200 or 400 i.u.	Parke Davis
TRIDESTRIN	Each tablet contains 500, 1000 or 5000 mouse units	Paines & Byrne
OESTRONE AMPOULES		
AMNIOTIN	1 mil contains 2000 or 10,000 i.u.	Squibb
FOLLICULAR SEX HORMONE	1 mil contains 25 or 50 rat units	Armour
GLANDUBOLIN	1 mil contains 100, 1000, 10,000 or 50,000 i.u.	Richter
KETODESTRIN	1 mil contains 500, 1000, 5000 or 10,000 i.u.	Paines & Byrne
MENFORMON	1 mil contains 100, 1000 or 10,000 i.u. Also 5 mil vials	Organon
OESTROGLANDOL	1 mil contains 1000 i.u.	Roche
OESTRONE	1 mil contains 10,000 or 50,000 i.u.	Ciba
PERLATAN	1 mil contains 500, 1000 or 10,000 mouse units. Also 10 mil vials	Boehringer
THEELIN (AQUEOUS) ..	1 mil contains 400 mouse units	Parke Davis
THEELIN IN OIL ..	1 mil contains 200 i.u.	Parke Davis
THELESTRIN	1 mil contains 1000, 2000, 5000 or 10,000 i.u.	Parke Davis
UNDEN	1 mil contains 2000 i.u.	G. W. Carrick
	1 mil contains 1000 i.u.	Bayer

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Name of Preparation	Description	Maker
OESTRONE CAPSULES AND TABLETS		
AMNIOTIN CAPSULES ..	Each capsule contains 1000 or 2000 i.u.	Squibb
GLANDUBOLIN TABLETS ..	Each tablet contains 100, 1000 or 3000 i.u.	Richter
HOGIVAL TABLETS ..	Each tablet contains 1000 i.u.	Camden
MENFORMON TABLETS ..	Each tablet contains 100, 500, 1000, 3000, 10,000 or 50,000 i.u.	Organon
OESTROGLANDOL ..	Each tablet contains 1000 i.u.	Roche
OESTRONE TABLETS ..	Each tablet contains 1000 or 10,000 i.u.	Hewlett
OESTRONE TABLETS ..	Each tablet contains 1000, 3000 or 10,000 i.u.	Paines & Byrne
OESTRIN TABLETS ..	Each tablet contains 1000 i.u.	Oxo
OVOSTAB TABLETS ..	Each tablet contains 1000 or 10,000 i.u.	Boots
PERLATAN TABLETS ..	Each tablet contains 500 mouse units	Boehringer
PROGYNON TABLETS ..	Each tablet contains 1000, 3000 or 10,000 i.u.	Schering
UNDEN PELLETS ..	Each pellet contains 100, 500 or 1000 i.u.	Bayer
OESTRONE MIXTURES		
ADYSMIN TABLETS ..	Each tablet contains ovarian residue 3 gr., oestrin 100 i.u., codeine phosphate 1/4 gr., yohimbine 1/12 gr.	Richter
ANTEOVIN AMPOULES ..	Each ampoule contains anterior lobe pituitary hormone 100 i.u. and ovarian follicular hormone 50 i.u.	Richter
ANTEOVIN TABLETS ..	Each tablet contains anterior lobe pituitary 3 gr. and ovarian follicular hormone 15 i.u.	Richter
CLIMATONE ..	Each tablet contains ovarian hormone 200 i.u. theobromine-calcium; calcium-lacticum; nitroglycerin; and menthol valerian	Paines & Byrne
GLANDITONE-O Tablets	Each tablet contains ovarian hormone 200 i.u. pituitary whole gland 1/20 gr., suprarenal 1/20 gr., thyroid 1/10 gr.	Richter
HORMOFORT OVARIAN TABLETS	Each tablet contains ovarian gland 1/8 gr., oestrone 100 i.u.	Richter
HORMOTONE "T" TABLETS	Each enteric-coated tablet contains desiccated suprarenal and whole pituitary 1/20 gr. each, desiccated thyroid 1/10 gr., ovarian follicular hormones therapeutically equivalent to 200 i.u.	Carnrick
MENOCRIN TABLETS ..	Each tablet contains ovarian gland 3 gr., thyroid gland extract 1/12 gr., anterior lobe pituitary 1/4 gr., oestrone 250 i.u.	Endocrines-Spicer
OVACOIDS TABLETS ..	Each tablet contains ovarian hormones equivalent to 5 gr. fresh gland, anterior pituitary hormones equivalent to 1/8 gr. fresh gland	Reed & Carnrick
OVARNON TABLETS ..	Each tablet contains 150 mg. desiccated ovary with 10 i.u. oestrone	Organon
PANESTRONE ..	Each tablet contains ovarian hormone 200 i.u. and desiccated suprarenal, pituitary and ovarian substance	Paines & Byrne
PROKLIMAN TABLETS ..	Each tablet contains 0.02 gm. "liposoluble ovarian extract" (Sistomensin) with sedative and laxative substances	Ciba
SISTOMENSIN AMPOULES	1 mil contains 0.05 gm. "liposoluble ovarian extract" (= 10 i.u. oestrone)	Ciba
SISTOMENSIN TABLETS ..	Each tablet contains 125 mgm. "liposoluble ovarian extract" (= 10 i.u. oestrone)	Ciba
OESTRONE PREPARATIONS		
AMNIOTIN PESSARIES ..	Each pessary contains 1000 or 2000 i.u.	Squibb
AMNIOTIN FOR NASAL USE	10,000 i.u. per mil or 20,000 i.u. in 30 mil	Squibb
KOLPON VAGINAL BOUGIES	Each bougie contains 500 i.u.	Organon
KOLPON VAGINAL TABLETS	Each tablet contains 1000 i.u.	Organon
MENFORMON DROPS ..	1 mil contains 10,000 i.u. in oil	Organon
MENFORMON OINTMENT	1 gm. contains 5000 i.u.	Organon
MENFORMON SUPPOSITORIES	Each suppository contains 1000 or 10,000 i.u.	Organon
OESTROGLANDOL OINTMENT	1 gm. contains 1000 i.u.	Roche
OESTRONE SUPPOSITORIES	Each suppository contains 1000 or 5000 i.u.	Paines & Byrne

Name of Preparation	Description	Maker
OESTRONE PREPARATIONS—<i>contd.</i>		
OESTROSALVE OINTMENT	1 oz. contains 10,000 i.u.	Paines & Byrne
OESTROSALVE OINTMENT (CONC.)	1 gm. contains 2500 i.u.	Paines & Byrne
PERLATAN SUPPOSITORIES	Each suppository contains 1000 mouse units	Boehringer
SOLESTRIN	1 mil contains 20,000 i.u.	Paines & Byrne
THEELIN VAGINAL SUPPOSITORIES	Each vaginal suppository contains 2000 i.u.	Parke Davis
THEELIN IN OIL FOR NASAL USE	1 mil contains 1000 i.u.	Parke Davis
UNDEN OINTMENT	1 gm. contains 5000 i.u.	Bayer
STILBOESTROL AMPOULES		
NEO-OESTRANOL—1	1 mil contains 0·5, 1 or 5 mgm.	Crookes
PABESTROL	1 mil contains 1 or 5 mgm.	Paines & Byrne
STILBOESTROL INJECTION SOLUTION—A. & H.	1 mil contains 1 or 5 mgm.	A. & H.
STILBOESTROL "AMPOULES"	1 mil contains 1 or 5 mgm.	Hewlett
STILBOESTROL—BOOTS	1 mil contains 1 or 5 mgm.	Boots
STILBOESTROL—B.D.H.	1 mil contains 1 or 5 mgm.	B.D.H.
STILBOESTROL—OXO	1 mil contains 1 or 5 mgm.	Oxo
STILBOESTROL "HYPOLOID"	1 mil contains 1 or 5 mgm.	B. Wellcome
STILBOESTROL PREPARATIONS		
NEO-OESTRANOL—1 (Nasal Spray)	1 mil contains 0·1 mgm.	Crookes
NEO-OESTRANOL—1, SALVE	1 gm. contains 0·1 mgm.	Crookes
NEO-OESTRANOL—1, PESSARIES	Each pessary contains 0·25 mgm.	Crookes
PABESTROL SUPPOSITORIES	Each suppository contains 2 mgm.	Paines & Byrne
PABESTROSALVE	1 gm. contains 1 mgm.	Paines & Byrne
SYNTESTRIN OINTMENT	1 oz. contains 15 mgm. stilboestrol dipropionate	Richter
"WELLCOME" STILBOESTROL OINTMENT	Each gramme contains 1/2 mgm. of stilboestrol dipropionate	B. Wellcome
STILBOESTROL TABLETS		
CLINESTROL	Each tablet contains 0·5, 1 or 5 mgm.	Glaxo
NEO-OESTRANOL TABLETS—1	Each tablet contains 0·1, 1 or 5 mgm.	Crookes
OVENDOSYN	Each tablet contains 0·5 mgm. stilboestrol with calcium phosphate 227 mgm.	Menley & James
PABESTROL	Each tablet contains 0·1, 0·5, 1 or 5 mgm.	Paines & Byrne
STILBOESTROL—A. & H.	Each tablet contains 0·5, 1 or 5 mgm.	A. & H.
STILBOESTROL—BOOTS	Each tablet contains 0·1, 0·5, 1 or 5 mgm.	Boots
STILBOESTROL—B.D.H.	Each tablet contains 0·5, 1 or 5 mgm.	B.D.H.
STILBOESTROL—HEWLETT	Each tablet contains 0·1 mgm. (Pink), 0·5 mgm. (White), 1 mgm. (Yellow), 5 mgm. (Orange)	Hewlett
STILBOESTROL—ORGANON	Each tablet contains 0·1, 0·5, 1·0 or 5 mgm.	Organon
STILBOESTROL—OXO	Each tablet contains 0·5, 1 or 5 mgm.	Oxo
STILBOESTROL "TABLOID"	Each tablet contains 0·25, 0·5, 1 or 5 mgm.	B. Wellcome
STILBOESTROL DIPROPIONATE AMPOULES		
NEO-OESTRANOL—11	1 mil contains 0·5, 1 or 5 mgm.	Crookes
PABESTROL D	1 mil contains 1 or 5 mgm.	Paines & Byrne
CLINESTROL	1 mil contains 1 or 5 mgm.	Glaxo
STILBOESTROL DIPROPIONATE—BOOTS	1 mil contains 1 or 5 mgm.	Boots
STILBOESTROL DIPROPIONATE "HYPOLOID"	1 mil contains 1 or 5 mgm.	B. Wellcome
STILBOESTROL DIPROPIONATE—B.D.H.	1 mil contains 1 or 5 mgm.	B.D.H.
SYNTESTRIN	1 mil contains 0·1, 0·25, 1 or 5 mgm.	Richter

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Name of Preparation	Description	Maker
STILBOESTROL DIPROPIONATE TABLETS		
NEO-OESTRANOL—11 ..	Each tablet contains 0.1, 1 or 5 mgm.	Crookes Paines & Byrne Boots
PABESTROL D ..	Each tablet contains 0.1, 0.5, 1 or 5 mgm.	
STILBOESTROL DISPRO- PIONATE—BOOTS	Each tablet contains 0.1, 0.5, 1 or 5 mgm.	
STILBOESTROL DIPRO- PIONATE—B.D.H.	Each tablet contains 0.5, 1 or 5 mgm.	B.D.H.
STILBOESTROL DIPRO- PIONATE "TABLOID"	Each tablet contains 1 or 5 mgm.	B. Wellcome
SYNTESTRIN	Each tablet contains 0.1, 0.25, 0.5, 1 or 5 mgm.	Richter
TESTICULAR EXTRACT PREPARATIONS		
ANDROSTIN TABLETS ..	Each tablet contains 1/2 i.u.	Ciba
ANDROSTIN AMPOULES ..	Ampoule A plus ampoule B represents active principles in 16 gm. fresh gland. (Ampoule B—3 i.u.)	Ciba
ERUGON PELLETS ..	Each pellet contains 0.25 units	Bayer Organon
TESTANON.. ..	Each tablet contains 50 mgm. of testicular desiccation	
TESTOSTERONE PROPIONATE AMPOULES		
NEO-HOMBREOL	1 mil contains 5, 10 or 25 mgm.	Organon
PERANDREN	1 mil contains 5, 10 or 25 mgm.	Ciba
STERANDRYL	1 mil contains 5, 10 or 25 mgm.	Roussel
TESTOSTERONE PRO- PIONATE	1 mil contains 1, 5 or 10 mgm.	Oxo
TESTOVIRON	1 mil contains 5, 10 or 25 mgm.	Schering Paines & Byrne
VIORMONE	1 mil contains 2 or 5 i.u. testosterone	
TESTOSTERONE PROPIONATE OINTMENTS AND SOLUTION FOR EXTERNAL USE		
ECTO-STERANDRYL ..	10 mil contains 50 mgm.	Roussel Organon
NEO-HOMBREOL OINT- MENT (weak)	1 gm. contains 2 mgm.	
NEO-HOMBREOL OINT- MENT (strong)	1 gm. contains 25 mgm.	Organon
PERANDREN OINTMENT ..	25 gm. contains 50 mgm. as testosterone	Ciba Schering Paines & Byrne
TESTOVIRON OINTMENT ..	25 gm. contains 50 mgm. (base)	
VIORMONE OINTMENT ..	1 oz. contains 60 mgm. or 150 mgm.	
TRIPHENYL CHLOROETHYLENE (SYNTHETIC) AMPOULES AND TABLETS		
GYNOSONE AMPOULES ..	Each ampoule contains 250 mgm.	I.C.I. I.C.I.
GYNOSONE TABLETS ..	Each tablet contains 200 mgm.	
TESTOSTERONE		
NEO-HOMBREOL (M) ..	Each tablet. contains 5 mgm. of methyl testosterone	Organon
METHYL TESTOSTERONE— BOOTS	Each tablet contains 5 mgm.	Boots
TESTOSTERONE PRO- PIONATE—BOOTS	Each ampoule contains 5, 10 or 25 mgm.	Boots
ETHISTERONE	Corpus Luteum Normine Each tablet contains 5 or 10 mgm. of anhydroxy-progesterone	Boots

NORMAL MEASUREMENTS IN RELATION TO AGE

AGE	Height (inches)				Weight (lb.)				Span (inches)				Upper Measurement (inches)				Lower Measurement (inches)				Circumference Measurements (inches)						AGE				
	M.		F.		M.		F.		M.		F.		M.		F.		M.		F.		M.		F.		M.			F.			
	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.		Min.	Max.		
Birth	19.3	21.1	19.0	20.8	6.2	8.6	6.4	8.6	18.1	20.1	18.1	19.9	12.1	13.1	12.1	13.1	6.9	7.9	13.9	13.6	13.8	13.6	13.4	13.2					Birth		
1 Mo.	20.9	22.9	20.5	22.5	9.0	11.8	8.4	11.0	20.1	22.1	19.5	21.5	13.3	14.3	13.0	14.0	7.7	8.7	15.2	14.9	14.3	14.1	13.8	13.6	1 Mo.					1 Mo.	
2 Mos.	22.1	24.1	21.7	23.7	10.4	13.6	9.8	12.6	21.0	23.0	20.4	22.4	13.9	14.9	13.6	14.6	8.1	9.1	16.0	15.7	15.6	15.3	15.2	15.0	2 Mos.					2 Mos.	
3 "	23.1	25.1	22.7	24.7	11.9	15.3	11.2	14.2	22.0	24.0	21.4	23.4	14.5	15.5	14.1	15.1	8.5	9.5	16.6	16.3	16.4	16.0	16.0	15.7	3 "					3 "	
4 "	24.0	26.0	23.6	25.6	13.2	16.8	12.4	15.8	22.9	25.1	22.3	24.3	15.0	16.0	14.7	15.7	9.0	10.0	17.0	16.7	16.9	16.5	16.5	16.2	4 "					4 "	
5 "	24.7	26.7	24.3	26.3	13.9	17.7	13.7	17.3	23.3	25.5	23.3	25.3	15.3	16.3	15.2	16.2	9.2	10.2	17.4	17.1	17.2	16.8	16.8	16.5	5 "					5 "	
6 "	25.4	27.4	25.0	27.0	15.2	19.4	14.3	18.1	24.3	26.5	23.8	25.8	15.9	16.9	15.5	16.5	9.6	10.6	17.7	17.3	17.5	17.0	17.1	16.8	6 "					6 "	
7 "	26.1	28.1	25.6	27.6	15.9	20.1	14.9	18.9	24.8	27.0	24.3	26.3	16.1	17.1	15.8	16.8	9.9	10.9	17.9	17.5	17.7	17.2	17.3	17.0	7 "					7 "	
8 "	26.6	28.6	26.1	28.1	16.5	20.9	15.6	19.6	25.3	27.5	24.8	26.8	16.3	17.5	16.0	17.0	10.0	11.2	18.1	17.7	17.9	17.4	17.5	17.2	8 "					8 "	
9 "	27.1	29.1	26.6	28.6	17.1	21.7	16.1	20.3	25.8	28.0	25.2	27.2	16.5	17.7	16.3	17.3	10.3	11.5	18.2	17.8	18.0	17.6	17.6	17.3	9 "					9 "	
10 "	27.6	29.6	27.1	29.1	17.6	22.4	16.6	21.0	26.2	28.4	25.7	27.7	16.8	18.0	16.4	17.6	10.5	11.7	18.4	18.0	18.2	17.8	17.7	17.4	10 "					10 "	
11 "	28.1	30.1	27.6	29.6	18.3	23.1	17.3	21.7	26.7	28.9	26.1	28.3	17.0	18.2	16.7	17.9	10.8	12.0	18.5	18.1	18.3	17.9	17.8	17.5	11 "					11 "	
12 "	28.4	30.6	28.0	30.0	18.9	23.9	17.8	22.4	27.2	29.4	26.6	28.8	17.3	18.5	16.9	18.1	11.0	12.2	18.9	18.6	18.2	18.5	18.1	17.9	17.6	12 "					12 "
13 "	29.6	31.8	29.1	31.3	20.1	25.3	18.9	23.7	28.2	30.4	27.6	29.8	17.8	19.0	17.4	18.6	11.5	12.7	18.9	18.5	18.8	18.4	18.2	17.9	15 "					15 "	
14 "	30.8	33.0	30.3	32.5	21.9	27.3	20.6	25.8	29.6	32.0	29.0	31.2	18.6	19.8	18.1	19.3	12.2	13.4	19.1	18.7	19.1	18.7	18.5	18.2	18 "					18 "	
15 "	31.7	34.1	31.3	33.6	23.1	28.7	21.7	27.1	30.6	33.0	29.9	32.3	18.9	20.3	18.6	19.8	12.7	14.1	19.3	18.9	19.4	19.0	18.7	18.4	21 "					21 "	
16 "	32.7	35.1	32.2	34.6	24.3	30.1	22.9	28.5	31.5	33.9	30.9	33.3	19.4	20.8	18.9	20.3	13.2	14.6	19.4	19.0	19.7	19.2	18.9	18.6	24 "					24 "	
17 "	34.5	36.9	33.9	36.3	26.1	32.3	24.7	30.7	32.9	35.5	32.4	34.8	20.0	21.4	19.6	21.0	14.1	15.5	19.6	19.2	20.2	19.6	19.2	18.9	30 "					30 "	
18 "	36.0	38.6	35.4	38.0	28.7	35.3	26.6	33.0	34.8	37.6	33.8	36.4	20.7	22.3	20.0	21.6	15.2	16.8	19.8	19.4	20.6	20.0	19.5	19.1	36 "					36 "	
19 "	37.4	40.2	36.9	39.5	30.5	37.5	28.6	35.2	36.3	39.1	35.2	38.0	21.3	22.9	20.6	22.2	16.1	17.7	19.8	19.6	21.0	20.4	19.8	19.3	42 "					42 "	
20 "	38.8	41.6	38.3	40.9	31.8	39.2	30.5	37.5	37.3	40.3	36.7	39.5	21.6	23.2	21.2	22.8	16.8	18.4	19.7	19.7	20.1	19.7	20.7	20.0	19.5	48 "					48 "

54 Mos.	40-1	42-9	39-5	42-3	33-8	41-6	32-5	39-9	38-8	41-8	38-2	41-2	22-0	23-8	21-5	23-3	17-7	19-5	17-7	19-5	20-3	19-9	21-7	21-0	20-2	19-7	54 Mos.
60	41-2	44-2	40-7	43-7	35-1	43-5	33-8	41-6	39-8	43-0	39-2	42-2	22-4	24-2	21-9	23-7	18-3	20-1	18-3	20-1	20-4	20-0	22-1	21-4	20-4	19-9	60
5½ Yrs.	42-4	45-4	41-9	44-9	37-4	46-4	35-9	44-5	41-3	44-5	40-7	43-9	22-7	24-7	22-4	24-2	19-3	21-3	19-3	21-1	20-4	20-1	22-4	21-7	20-6	20-0	5½ Yrs.
6	43-5	46-5	43-1	46-1	39-2	48-6	37-5	46-5	42-4	45-6	41-7	44-9	23-0	25-0	22-6	24-6	20-0	22-0	19-9	21-1	20-5	20-1	22-7	22-0	20-9	20-2	6
6½	44-5	47-7	44-2	47-2	41-0	50-8	39-2	48-8	43-4	46-8	42-8	46-0	23-3	25-3	23-0	25-0	20-7	22-7	20-5	22-5	20-5	20-2	23-0	22-3	21-1	20-4	6½
7	45-6	48-8	45-2	48-4	43-0	53-2	42-1	52-3	44-5	47-9	44-3	47-7	23-5	25-7	23-4	25-4	21-3	23-5	21-6	23-6	20-6	20-3	23-3	22-7	21-3	20-5	7
7½	46-6	49-8	46-3	49-5	45-0	55-8	44-1	54-9	45-5	49-1	45-4	48-8	23-8	26-0	23-7	25-9	22-0	24-2	22-1	24-3	20-7	20-3	23-7	23-0	21-5	20-7	7½
8	47-5	50-9	47-2	50-6	47-2	58-4	46-4	57-6	46-8	50-4	46-5	49-9	24-1	26-3	24-0	26-2	22-7	24-9	22-8	25-0	20-7	20-4	24-0	23-4	21-8	20-8	8
8½	48-5	51-9	48-2	51-6	49-3	61-3	48-6	60-6	48-0	51-6	47-5	51-1	24-5	26-7	24-4	26-6	23-3	25-5	23-4	25-6	20-8	20-5	24-3	23-8	22-0	21-0	8½
9	49-5	52-9	49-2	52-6	51-6	64-4	51-0	63-8	49-1	52-9	48-6	52-2	24-7	27-1	24-7	26-9	23-9	26-3	24-1	26-3	20-9	20-5	24-6	24-2	22-3	21-2	9
9½	50-4	54-0	50-1	53-7	54-2	67-8	53-6	67-2	50-3	54-1	49-6	53-4	25-1	27-5	25-0	27-4	24-5	26-9	24-6	27-0	20-9	20-6	25-0	24-6	22-5	21-5	9½
10	51-4	55-0	51-2	54-8	57-0	71-6	56-2	71-0	51-4	55-4	50-7	54-5	25-5	27-9	25-5	27-9	25-1	27-5	25-1	27-5	21-0	20-7	25-3	25-0	22-8	21-8	10
10½	52-4	56-0	52-3	55-9	59-9	75-5	59-3	75-1	52-5	56-5	51-7	55-7	25-7	28-3	25-8	28-4	25-7	28-3	25-6	28-2	21-0	20-8	25-7	25-5	23-0	22-1	10½
11	53-3	57-1	53-4	57-2	63-0	79-4	63-7	81-1	53-5	57-7	53-3	57-3	26-1	28-7	26-5	29-1	26-3	28-9	26-4	29-0	21-1	20-9	26-1	26-1	23-3	22-4	11
11½	54-3	58-1	54-6	58-4	66-2	83-2	66-9	85-5	54-6	58-8	54-2	58-4	26-5	29-1	26-9	29-5	26-9	29-5	27-0	29-6	21-2	20-9	26-6	26-6	23-6	22-8	11½
12	55-2	59-0	55-6	59-6	69-4	87-2	70-7	90-5	55-8	60-0	55-4	59-6	27-0	29-6	27-4	30-0	27-4	30-0	27-5	30-1	21-2	21-0	27-0	27-1	23-9	23-2	12
12½	56-0	60-0	56-7	60-7	72-7	91-3	74-5	95-7	56-9	61-3	56-4	60-6	27-3	30-1	27-7	30-5	27-9	30-7	28-0	30-8	21-3	21-1	27-5	27-6	24-2	23-6	12½
13	56-9	60-9	57-7	61-7	75-9	95-7	78-7	101-3	58-0	62-4	57-6	61-8	27-7	30-5	28-2	31-0	28-5	31-3	28-5	31-3	21-4	21-2	28-0	28-1	24-6	23-9	13
13½	57-8	61-8	58-5	62-7	79-3	100-3	83-6	107-2	59-0	63-6	58-6	63-0	28-2	31-0	28-8	31-6	29-0	31-8	28-9	31-8	21-5	21-3	28-6	28-5	25-0	24-2	13½
14	58-6	62-8	59-3	63-5	81-1	102-9	89-3	113-5	59-6	64-2	59-1	63-5	28-4	31-2	29-2	32-0	29-3	32-1	29-6	32-3	21-6	21-4	29-1	28-9	25-4	24-5	14
14½	59-5	63-7	59-9	64-1	85-0	108-0	92-4	116-6	60-7	65-3	60-2	64-6	28-8	31-8	29-5	32-3	29-7	32-7	29-7	32-5	21-7	21-5	29-7	29-3	25-9	24-7	14½
15	60-3	64-5	60-4	64-6	89-4	113-4	95-7	119-7	61-7	66-5	60-7	65-3	29-3	32-3	29-8	32-6	30-2	33-2	29-9	32-7	21-8	21-6	30-3	29-6	26-4	24-8	15
15½	61-1	65-3	60-8	65-0	91-6	116-2	99-0	122-8	62-3	67-1	61-3	65-9	29-5	32-5	30-1	32-9	30-5	33-5	30-1	32-9	21-9	21-7	31-0	29-9	26-8	25-0	15½
16	61-8	66-2	61-1	65-3	96-0	122-0	99-0	122-8	63-4	68-2	61-3	65-9	30-0	33-0	30-1	32-9	31-0	34-0	30-1	32-9	22-0	21-7	31-7	30-1	27-2	25-1	16
16½	62-5	66-9	61-4	65-6	98-4	125-0	102-5	125-9	63-9	68-9	61-9	66-5	30-3	33-3	30-4	33-2	31-2	34-2	30-3	33-1	22-1	21-8	32-3	30-3	27-5	25-2	16½
17	63-2	67-6	61-6	65-8	103-8	131-6	102-5	125-9	65-0	70-0	61-9	66-5	30-7	33-7	30-4	33-2	31-8	34-8	30-3	33-1	22-2	21-8	32-9	30-5	27-8	25-3	17
17½	63-8	68-2	61-8	66-0	106-8	135-2	106-1	128-9	65-6	70-6	62-5	67-1	31-0	34-0	30-7	33-5	32-0	35-0	30-5	33-3	22-3	21-8	33-3	30-7	28-0	25-4	17½
18	64-4	68-8	61-9	66-1	109-8	139-0	106-1	128-9	66-1	71-1	62-5	67-1	31-3	34-3	31-6	34-6	32-4	35-2	35-2	33-3	22-4	21-9	33-7	30-8	28-2	25-5	18
18½	64-9	69-3	62-0	66-6	113-3	142-3	107-2	128-9	66-6	71-8	63-0	67-1	31-6	34-6	31-9	34-9	32-6	35-4	35-4	33-3	22-4	21-9	34-1	30-8	28-4	25-5	18½
19	65-3	69-7	62-3	67-1	117-2	145-6	107-2	128-9	67-2	72-4	63-0	67-1	31-9	34-9	32-1	35-3	32-7	35-9	35-9	33-3	22-5	21-9	34-6	30-9	28-5	25-6	19
19½	65-6	70-0	62-6	67-4	121-5	148-5	107-2	128-9	67-8	73-0	63-0	67-1	32-1	35-3	32-1	35-3	32-7	35-9	35-9	33-3	22-5	21-9	34-6	30-9	28-6	25-6	19½
20	65-8	70-2	62-8	67-6	121-5	148-5	107-2	128-9	67-8	73-0	63-0	67-1	32-1	35-3	32-1	35-3	32-7	35-9	35-9	33-3	22-5	21-9	34-7	31-0	28-7	25-7	20

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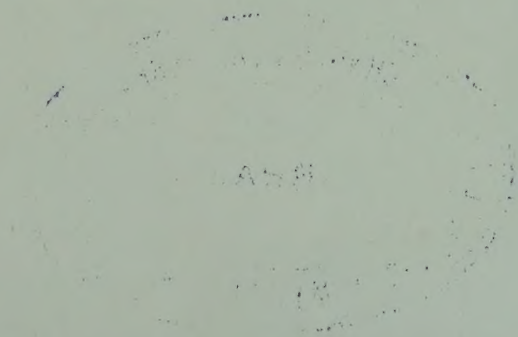
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